NEURO-ENDOCRINE ACTIVATION AND INHIBITION IN HEART FAILURE

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DEDICATION

To My Mother and My Wife without who waited patiently for the completion of this work.

SUMMARY

The idea of vasodilator therapy for heart failure has been toyed with for almost one hundred years, possibly more. In the mid-twentieth century nitrates attained a definite role in the management of acute pulmonary oedema. There is little doubt that vasodilators can improve central haemodynamics acutely. However, during the 1970's investigators started to apply physiological principles of preload and afterload reduction to the management of chronic heart failure. The results were largely disappointing, either because tolerance occurred to the vasodilator actions of the drugs, or because vasodilatation is an ineffective mode of treatment for chronic heart failure. When work on this thesis started disillusionment was setting in regarding the efficacy of chronic vasodilator therapy for patients with heart failure.

Although increases in plasma renin were first demonstrated in heart failure almost 50 years ago, there are few studies which have investigated the haemodynamic and metabolic correlates of renin-angiotensin-aldosterone system activation in detail. The present work indicates that patients with heart failure have a depletion of total body potassium and an excess of total body sodium when compared to normal subjects or patients with mild untreated hypertension. This depletion in potassium is not related to a reduction in lean body mass. Within the group of patients with heart failure elevated plasma concentrations of active renin were associated with a lower arterial pressure, lower serum concentrations of sodium and potassium and more

marked depletion of total body potassium. Arterial pressure appears to be an important determinant of renin secretion in heart failure. Although the electrolyte disturbances are probably largely a consequence of increased plasma concentrations of renin and angiotensin II, mediated through aldosterone and antidiuretic hormone, depletion of serum sodium and potassium may further stimulate renin secretion.

The renin-angiotensin, sympathetic and parasympathetic nervous systems are closely integrated. Angiotensin II can stimulate sympathetic activity in several ways, but can also reduce parasympathetic activity. The present work confirms that patients with heart failure have elevated sympathetic activity at rest, but reduced parasympathetic and sympathetic reflex activity as has been previously shown. This thesis also shows that at maximal exertion patients with heart failure have evidence of reduced sympathetic activity compared to normal subjects, and that this is related to the intensity rather than duration of exercise.

In view of the disturbances in haemodynamic function, autonomic activity and cellular metabolism in heart failure it is not surprising to find a high frequency of arrhythmias. These arrhythmias are directly related to plasma concentrations of renin and noradrenaline, though whether this is a causal relationship or by association with the severity of ventricular dysfunction is controversial. The present study found a poor relationship

between the severity of ventricular dysfunction and the frequency of arrhythmias in a group of patients with generally poor ventricular function.

Using two double-blind cross-over studies the angiotensin-converting enzyme inhibitors captopril and enalapril were shown to improve symptoms and exercise performance over a 6-8 week period. The study on captopril constituted one of the first placebo-controlled investigations in the literature to establish the efficacy of angiotensin-converting enzyme inhibitors in chronic heart failure. The paper on enalapril established that this was a class effect. These studies demonstrated that angiotensin-converting enzyme inhibitors could correct hypokalaemia and total body potassium depletion, but did not have a major impact on serum or total body sodium. Angiotensin-converting enzyme inhibitors also reduced plasma levels of noradrenaline, suggesting reduced sympathetic activity, and improved parasympathetic reflex responsiveness. Not surprisingly angiotensin-converting enzyme inhibitors also reduced the frequency of ventricular arrhythmias.

Studies were performed to investigate the effects of angiotensin-converting enzyme inhibitors on renal function in greater detail, and their interaction with frusemide. These indicated that introduction of angiotensin-converting enzyme inhibitor led to a reduced diuresis, plasma volume expansion and a fall in serum sodium. Urinary potassium losses were reduced and serum potassium unaltered in the short term. Renal blood flow tended to increase and

glomerular filtration rate to fall; these effects were enhanced by concomitant administration of frusemide. Studies on renal tubular function indicated increased proximal tubular water and sodium reabsorption as the likely cause for the reduced diuresis in response to frusemide. Longer term studies indicate that angiotensin-converting enzyme inhibitors cause a consistent fall in glomerular filtration rate and increase in renal blood flow while the filtration fraction is reduced towards normal. Withdrawal of the angiotensin-converting enzyme inhibitor leads to a rapid return of glomerular filtration to baseline levels, but renal blood flow appears elevated for some time after withdrawal, suggesting structural change in the vasculature or prolonged tissue enzyme inhibition.

Heart failure and angina pectoris commonly co-exist but the effects of angiotensin converting enzyme inhibitors had not been studied previously in such patients. The present study indicates that captopril may reduce the angina threshold. The reduction in coronary perfusion pressure appears to offset the potential beneficial effects on myocardial oxygen consumption of the reduction in preload and afterload. However, the frequency of ventricular arrhythmias was also reduced in this study.

Finally an attempt was made to determine if angiotensin-converting enzyme inhibitors had had a beneficial effect on prognosis in patients with heart failure. This was an open non-randomised evaluation. Computer modelling was used to try and correct for differences in the distribution of

adverse prognostic factors between those receiving an angiotensin-converting enzyme inhibitor and those not. A non-significant trend to improved prognosis in those receiving captopril or enalapril was noted. However, there was an excess of vascular deaths in the group treated with an angiotensin-converting enzyme inhibitor, but small numbers make these findings of uncertain significance.

Angiotensin-converting enzyme inhibitors are a new modality for the treatment of chronic heart failure. The work presented in this thesis has helped establish their usefulness and limitations, and demonstrated that they are more than mere vasodilator agents. The reason for their efficacy remains to be established. Perhaps it is because they induce haemodynamic tolerance infrequently. However, correction of intra-cellular electrolyte disturbances and autonomic dysfunction could be at least as important.

PART ONE HISTORICAL INTRODUCTION

CHAPTER 1: HISTORICAL PERSPECTIVES

RENIN AND ANGIOTENSIN

The hormone renin was first discovered by Tigerstedt and Bergman in 1898.[1] They showed that extracts of rabbit renal cortex caused marked and prolonged increases in blood pressure. Little further progress was made for 30 years. In the 1930's Goldblatt's experiments[2] demonstrating that renal artery constriction could lead to sustained hypertension stimulated a further search for a pressor substance secreted by the kidney, which finally led to the re-discovery of renin.[3] However, it was soon realised that renin was not inherently a vasoactive substance. Friedman[4] found that in an isolated dog's tail preparation renin did not cause vasoconstriction directly and that an intermediate substance must be responsible. Kohlstaedt et al [5] and Munoz et al [6] suggested that and subsequently Braun-Menendez[7] and Page and Helmer[8] showed that renin acted as an enzyme to produce a substance that had a short-lived but powerful vasoconstrictor effect. They called it hypertensin or angiotonin but subsequently it became known as angiotensin. It was around this time that Merril first noted that there was an increased concentration of renin in the renal veins of patients with heart failure.[8a] Later, it was shown that if renin was incubated with plasma

in the absence of chloride ions, a decapeptide was formed, which was named angiotensin I.[9] Chloride ions activated a dipeptidyl carboxypeptidase, which subsequently became known as the angiotensin-converting enzyme, that removed 2 amino acids from the C-terminal to produce angiotensin II, the most powerful component of the renin-angiotensin cascade.[10,11,12] The story was completed by the identification of a large alpha-globulin protein synthesised in the liver which was called the renin substrate or angiotensinogen.[13]

Originally, the plasma was thought to be the main site of formation of angiotensin II, but subsequently the kidney and lung were found to be major sites of conversion.[14,15] It is now realised that many, if not all, tissues have the ability to convert angiotensin I to angiotensin II. The converting enzyme appears to be bound to the vascular endothelium of many tissues, and is probably the major source of plasma converting enzyme.[16]

Angiotensin II is extracted across the kidney, the limbs, and the splanchnic circulation, though the proportions due to receptor binding and metabolism are unknown. Aminopeptidase enzymes are largely responsible for angiotensin II degradation. One heptapeptide fragment, angiotensin III, may retain some biological activity.[17]

ALDOSTERONE

As early as 1941, Raab reported that the blood level of adrencortical hormones was elevated in heart failure[18] while in patients with heart failure the concentration of sodium was noted to be lower in faeces, sweat and saliva.[19-22]

In 1950, Deming and Leutscher[23] noted that urine extracts from patients with congestive cardiac failure contained a substance with potent sodium-retaining activity which they identified as an adrenal steroid. This was later isolated and characterised as aldosterone.[24,25]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Though it has been possible to interfere with the effects of angiotensin II by the use of "inactive" structural analogues for 30 years, progress in understanding the consequences of such an intervention was hampered by the need for intravenous infusions and the partial agonist activity of the analogues.[26,27] Ferreira in 1965 discovered a bradykinin-potentiating factor in the venom of the Brazilian pit viper, Bothrops jararaca.[28] Later the venom was also shown to inhibit the angiotensin-converting enzyme.[29] Isolation, purification, sequencing and synthesis led to the first potent specific angiotensin-converting (ACE) inhibitor, teprotide.[30] Unfortunately, this was inactive orally, but a programme of drug development subsequently led to the discovery of captopril. The number of ACE inhibitors now given to man runs into two figures.

All these compounds depend in part for their activity on the formation of ligands with the tightly-bound zinc ion of the enzyme.[31] However, it appears that these compounds do not have the ability to chelate free zinc ions or to remove the ion from metaloproteins.

RENIN INHIBITORS

Renin's only known effect is to catalyse the production of angiotensin I from its precursor[32]. This is the rate-controlling step in the production of angiotensin II.[33] In contrast, the angiotensin-converting enzyme has a number of other substrates including bradykinin, enkephalin and perhaps neurotensin and substance P.[34] Inhibition of angiotensin-converting enzyme is therefore less specific. Also, the angiotensin-converting enzyme is not the rate-limiting step in the production of angiotensin II, therefore almost complete inhibition is needed to reduce plasma levels of angiotensin II. Moreover, other enzymes such as cathepsin G and tonin may act upon angiotensin I to produce angiotensin II.[35,36] However, despite some promising work in normal volunteers,[37] no renin inhibitor is generally available for study in patients with heart failure at present.

SUMMARY

Development of orally effective ACE inhibitors has permitted a much better understanding of the role of the renin-angiotensin-aldosterone system in heart failure. The introduction of new inhibitors of renin and angiotensin II receptor antagonists will help to elucidate more precisely which action(s) of the ACE (angiotensin-converting enzyme inhibitors) is (are) most important in mediating their beneficial as well as adverse effects.

CHAPTER 2: PHYSIOLOGICAL CONTROL OF THE COMPONENTS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

A) RENIN

Renin is first synthesised as a high molecular weight protein, preprorenin. This is metabolised to inactive prorenin (molecular weight 55,000 Daltons), which may then, in certain tissues, be converted to active renin (molecular weight 44,000 Daltons).[38] Many tissues have the capacity to process this into the active compound (eg;human chorionic cells).[39]

Circulating renin originates largely from the kidney where it is synthesised and stored in the juxtaglomerular cells of the afferent glomerular arteriole of the kidney.[40-42]

Five basic mechanisms controlling renin release have been described. They are:

1) an intrarenal baroreceptor
2) the amount of sodium (or possibly chloride) ion sensed by the macula densa segment of the distal tubule
3) the sympathetic innervation of the kidney and humorally released catecholamines
4) hormonal factors, including angiotensin II, prostaglandins and atrial natriuretic peptide
5) plasma potassium and calcium.

Intrarenal Baroreceptors

That renin could be released by a reduction in renal perfusion pressure was first alluded to by Kohlstaedt et al in 1940,[43] though this was originally attributed to a reduction in pulse pressure rather than mean perfusion pressure. Tobian et al in 1959 were the first to suggest the existence of an intrarenal baroreceptor that increased renin secretion in response to a reduction in mean perfusion pressure,[44] which was later confirmed by Skinner et al.[45] Tobian also noted that juxtaglomerular cell granulation decreased with an increase in renal perfusion pressure.[44]

Renin release in response to hypotension was found still to occur, despite removal of the influence of the macula densa, sympathetic nerves and adrenal hormones.[46,47] But papaverine, which blocks renal auto-regulation at the afferent arteriole, was shown to prevent haemorrhage-induced renin secretion from denervated, non-filtering kidneys in anaesthetised dogs, suggesting a role for the afferent arteriole in renin secretion.[48]

The theory formulated was that high renal perfusion pressure or afferent renal arteriolar vasodilatation would stretch the vascular wall, leading to stretch of the juxtaglomerular cells located in the media of the afferent arteriole[49] and that this would lead to a decrease in renin

release. However, several investigators noted that experimental models of renal (and systemic) hypotension led to renal vasodilatation, sufficient to maintain blood flow, concurrent with increased renal renin secretion.[50,51] This renal auto-regulation in response to hypotension still occurred in the presence of renal vasoconstriction produced by intrarenal infusion of angiotensin II, or noradrenaline or an increase in sympathetic nerve discharge.[52,53] In the light of these experiments, Vander[54] proposed that a decrease in transmural pressure, a decrease in intramural tension, or a reduction in intravascular pressure was the stimulus to renin secretion. Kaloyanides et al demonstrated that clamping the ureter, a manoeuvre that increases renal interstitial pressure, caused a rise in renin secretion that could be reversed by increasing the renal perfusion pressure.[55] This supports the notion that transmural pressure gradients rather than changes in afferent arteriolar diameter regulate renin release. Of note, maximal renin secretion appeared to occur at the time of maximal afferent arteriolar vasodilatation, whether induced by ureteric occlusion or hypotension.[56] However, other experiments [57] showed that at a fixed perfusion pressure and at an assumed constant interstitial pressure, vasodilatation with papaverine reduces renin secretion and vasoconstriction with phenylephrine increases it. This suggests that changes in afferent arteriolar radius may after all be important in the release of renin.

Initial reports of an effect of indomethacin on auto-regulation have not been confirmed.[58,59] However, renin release in response to hypotension within the auto-regulatory range is inhibited by indomethacin, suggesting an important role for prostaglandin- mediated renin release.[60] Renin release in response to more profound hypotension is not inhibited by indomethacin.

A rise in interstitial pressure induced by ureteric occlusion also induces prostaglandin E_2 production, while indomethacin can prevent the associated renal vasodilatation and renin release.[61,62]

Autonomic Nervous System

In 1952, De Muylder identified nerves travelling to the afferent renal arterioles and the juxtaglomerular cells.[63] These were later identified as sympathetic in origin.[64,65] A cholinergic nerve supply to the kidney is more controversial.[66] Vander first noted that stimulation of renal nerves could release renin.[67] It was later demonstrated that this could be blocked by propranolol.[68] It was not clear whether these effects were due to changes in afferent arteriolar tone, changes in sodium content at the macula densa or direct. However, using the non-filtering, papaverine-treated kidney, it was shown that renin release occurred independent of changes in haemodynamics and sodium metabolism.[69] Alpha-adrenergic inhibition in contrast caused an increase in renin secretion by haemodynamic mechanisms.[68]

The afferent signals and central control of renal sympathetic nervous activity have also been intensively investigated. Studies on the brainstem in dogs and cats suggest that the sympathetic nervous system has a "tonic" stimulatory effect on renal renin secretion.[70,71] Renal sympathetic nervous activity has been shown to be inversely related to carotid sinus pressure,[72,73], and a reduction in carotid sinus pressure may lead to a rise in renin.[74] Vagally-innervated cardiopulmonary receptors have also been identified that inhibit renin release.[75] Interpretation of early studies showing an inverse relationship between changes in atrial pressure and renin release are hampered by a lack of knowledge of atrial natriuretic peptide, but suggest a neural component mediated by vagal afferents.[76,77] It thus appears that:

1) cardiopulmonary receptors with vagal afferent pathways tonically inhibit renal release and can respond to a decrease in central blood volume that does not activate baroreceptors.

2) these reflexes may be modified by tonic inhibition from carotid baroreceptors.[78,79]

3) the efferent limb of these reflexes is via sympathetic innervation.[79,80]

Circulating Catecholamines

Infusion of both noradrenaline and adrenaline may stimulate renin release,[67,81] though intravenous infusions of noradrenaline may actually reduce renin as a result of the increase in arterial pressure. The stimulation of renin secretion persists in the non-filtering kidney model, even when papaverine is used to reverse renal vasoconstriction.[69] Propranolol but not alpha-adrenergic receptor blockade prevents renin release by sympathetic stimuli[82] and renin release appears to be predominantly mediated through the beta-1 receptor.[83-85] Stimulation of alpha receptors may cause renal vasoconstriction and indirectly induce renin release.[86] However, others have found that alpha-adrenergic stimulation may inhibit renin release,[87,88] while alpha-adrenergic receptor antagonists may increase circulating renin.[89] Low dose infusions of noradrenaline in one experiment were found to inhibit renin release while higher doses stimulated renin secretion.[90] This could be due to stimulation of pre-synaptic alpha-receptors which reduce noradrenaline and hence renin release, while at higher doses post-synaptic $beta_1$ receptors are stimulated.[91,92] In-vitro studies confirm that beta-adrenergic stimuli lead to renin secretion, but an effect mediated through alpha-receptors is controversial.[93,94]

Dopamine also stimulates renal renin release,[95-98] which can be blocked by haloperidol but not propranolol. However, changes in renal blood flow may override this effect.

Parasympathetic Nervous System

Acetylcholinesterase-containing fibres have been identified within the kidney,[99] but renal sympathetic nerves have been shown to contain acetylcholinesterase.[66] Atropine can prevent the increase in renal plasma flow, urine volume, and sodium and potassium excretion caused by acetylcholine.[100] However, no change in renal renin secretion has been noted with infusions of acetylcholine[101] or when incubated with rat renal slices in-vitro.[102]

The Macula Densa and Sodium Metabolism

The macula densa region of the distal tubule, at the boundary of the ascending limb of the loop of Henle and the distal tubule, is in close contact with the juxtaglomerular cells of the afferent arteriole.[103,104] This intimate relationship has suggested that renin may in some way control individual nephron glomerular filtration rate.[105]

In 1963, Brown et al noted that sodium depletion could cause renin release in man.[106] Sodium deprivation leads to an increase in proximal tubular sodium reabsorption[107,108] and a decrease in the sodium load (the product of sodium concentration and tubular flow rate) to the macula densa. Osmotic diuretics, by restoring the distal tubular sodium load, can override the effects of hypotension on renal renin release.[109] Volume expansion by hypotonic saline

results in a reduced fractional excretion of sodium and an increase in renin, which can be reversed if isotonic saline is infused into the renal artery but only in the kidney ipsi-lateral to the infusion,[110] indicating that the filtered sodium load or the sodium concentration at the afferent arteriole is important in controlling renin. In micropuncture studies in rats, diuresis induced by saline or mannitol has been shown to suppress renin secretion and increase the distal tubular sodium load, but the distal tubular sodium concentration was increased by saline and reduced by mannitol, indicating that sodium load rather than concentration may be more important.[111] Studies with non-filtering kidneys have suggested that hypertonic saline does not suppress renin release by non-tubular mechanisms,[112] and some studies on rat renal cortical slices have failed to show an increase in renin release if osmolality is kept constant,[113] though others have noted an increase in renin release with increasing sodium concentration in the perfusate.[114,115]

In the intact kidney, increased plasma osmolality and oncotic pressure may both increase plasma renin, though the mechanisms may be different. The former may alter juxtaglomerular cell volume[116] and the latter glomerulo-tubular balance to reduce the delivery of sodium to the distal tubule.[117]

Volume expansion alone does not appear to reverse the

activation of the renin-angiotensin system caused by sodium depletion.[118-120] Saline suppression of renin release is due primarily to increased tubular sodium transport, rather than volume expansion.

However, Kotchen has suggested that the chloride ion rather than sodium may be more important in renal renin control,[121] at least in the rat, though this could not be confirmed in dogs.[122]

Potassium

Potassium chloride infused into the renal artery suppresses renin secretion, with an increase in potassium ion concentration as small as 0.5 mmol/l,[123] but this also caused increased sodium excretion. This effect is not seen in non-filtering kidneys.[112] Potassium also does not appear to increase renin secretion in-vitro.[113] Dietary potassium depletion in dogs has been shown to cause hypokalaemia and stimulate plasma renin in the absence of a change in plasma sodium.[124] Others have reported similar results and an increase in renal prostaglandin synthesis.[125] A high dietary potassium has also been shown to block the rise in renin associated with sodium depletion in rats.[126] However, studies with potassium bicarbonate rather than chloride have not reproduced these results,[127] perhaps because the increase in potassium is attenuated by the alkalosis. Potassium given with lactate or sulphate as the anion does appear to suppress renin.[122]

Dietary potassium supplementation also reduces plasma renin in salt-deprived normal human subjects[128] and in patients with hypertension on a normal sodium diet,[129] generally accompanied by increases in plasma potassium. However, an acute infusion of potassium to achieve similar in creases in plasma potassium does not suppress renin in sodium-deplete subjects, although it does appear to enhance the ability of sodium repletion to suppress renin.[130,131]. Others have suggested that adrenal steroids may be necessary for the effects of potassium on renin secretion,[132] but as potassium loading induces a marked natriuresis in Addisonian patients,[133] it is difficult to test in man.

Calcium

Calcium can inhibit sodium reabsorption,[134] alter blood pressure[135] and catecholamine release.[136] Therefore, it is difficult to assess the role of calcium on renin release. In-vitro, calcium suppresses renin secretion, while the suppression of renin by angiotensin II does not occur in the absence of calcium[137], in contrast to sympathetically-mediated renin release.[138] Acute and chronic hypocalcaemia does not appear to affect plasma renin in man,[139] though intravenous injections of calcium chloride can reduce renin.[140] Verapamil infused intrarenally reduces renin release in the intact kidney; the reverse is seen in the papaverine-treated, non-filtering kidney,[141] suggesting that haemodynamic effects reverse an inhibitory effect of verapamil.

Magnesium

Magnesium chloride infused into the renal arteries of dogs causes renin release.[142] However, the intravenous infusion of magnesium sulphate to salt-deplete human subjects did not alter plasma renin.[140] In-vitro experiments have also failed to show an effect of magnesium on renin release.[143]

Angiotensin II

Vandel and Geelhoed[144] first demonstrated that angiotensin II could suppress renin secretion in the absence of a change in renal perfusion pressure in dogs. DeChamplain subsequently noted that subpressor doses of angiotensin II could suppress renin in normal and hypertensive humans.[145]

There are two mechanisms by which angiotensin II can reduce renin. Firstly, a "short" feedback loop, by a direct effect on the juxtaglomerular cells[146] and, secondly, by a "long" loop through stimulation of aldosterone and volume expansion. The direct effects appear calcium-dependent, at least in part.[137] Angiotensin II powerfully reduces the effects of sympa thetic activation and frusemide on renin secretion.[147,148] Reducing angiotensin II formation by inhibiting the converting enzyme leads to a prompt rise in renin.

Anti-diuretic Hormone

Anti-diuretic hormone (ADH) suppresses renin secretion in animal models,[149] even in non-filtering kidneys.[150] Plasma renin is elevated in diabetes insipidus[151] and can be suppressed by infusions of ADH in both normal subjects and patients.[152,153] However, these effects are probably mediated through indirect effects on plasma volume.

Prostaglandins

Early studies in dogs and man failed to show consistent effects of prostaglandins of the E series on renin release[154,155] and in-vitro studies failed to show a direct effect on renin production.[156] However, later in-vitro studies on prostacyclin did show direct stimulation of renin.[158] Subsequent studies in dogs showed that renin was also released by prostaglandin E[158] and that this was not mediated by the sympathetic nervous system or the macula densa.[159] Moreover, indomethacin administered to the salt-deplete, renally denervated, dog model induced a fall in renal blood flow, glomerular filtration rate and renin secretion.[160] Prostacyclin has also been shown to stimulate renin release in intact animal models and man.[161,162] Other prostaglandins like prostaglandin F_{2alpha} may inhibit renin release in-vitro.[163]

An alternative mechanism by which prostaglandins could stimulate renin release is by elevating renal interstitial pressure.[164,165]

Atrial Natriuretic Peptide

Atrial natriuretic peptide is directly related to atrial pressure (or perhaps transmural tension), and serves as a further mechanism linking atrial pressures to renin secretion.[166,167] The direct effect of atrial natriuretic peptide is to inhibit the release of renin,[168-170] aldosterone,[170-171] and anti-diuretic hormone.[172] The associated natriuresis, by increasing the distal tubular sodium load, should also favour renin suppression by an effect on the macula densa.

However, some clinical studies have failed to demonstrate an effect of atrial natriuretic peptide on renin release. Vasodilatation, hypotension and a relative reduction in plasma volume might stimulate renin, while increased transudate of solutes into the renal parenchyma could raise tissue pressures, resulting in renin stimulation.

Cardiac Glycosides

Digoxin is widely prescribed in heart failure. Several studies have reported that it may reduce plasma renin[173] and inhibit renal renin release by frusemide.[174] The mechanism is obscure but Thames suggested that acetylstrophanthidin caused a reflex reduction in renal sympathetic activity via vagal afferents.[175] However, others have suggested that glycosides may alter the intracellular sodium content of the macula densa,[176] thereby inhibiting renin release.

DIURETICS

"Loop" diuretics

Loop diuretics inhibit the active co-transport of chloride in the thick ascending limb of the loop of Henle; sodium reabsorption appears to follow the ionic gradient passively.[177-180] This effect may also occur at the macula densa.[181] These agents also cause in increase in renal blood flow, specifically to the renal cortex, and can override renal auto-regulation.[182-184] The haemodynamic effects appear to be prostaglandin-mediated.[185,186]

Frusemide increases plasma renin in man,[187,188] though the mechanism is disputed. Reduction in plasma volume may increase renin, but when the frusemide-induced volume loss is replaced, plasma renin still rises.[189,190] Others have shown a bi-phasic release of renin by frusemide, the late, but not the early, in crease can be prevented by fluid replacement.[190,191] In animal studies, the early rise in renin is not blocked by propranolol or enhanced by aminophylline,[192] but the late increase may be reduced by sympathetic denervation and propranolol.[191,193]. However, in studies of unilateral renal sympathetic denervation, the stimulatory effect of small (0.5 mg/kg), but not large (6 mg/kg), intravenous doses of frusemide on renin was reduced in the denervated kidney.[194] The effects of the smaller dose could be mediated by venodilatation de-activating cardiac vagal afferents and increasing renal sympathetic activity,[195] while larger doses had a direct renal effect. In man,

propranolol and metoprolol can both inhibit the diuretic-induced increase in renin.[196,197] But, renin release under these circumstances may be accompanied by and due to a concomitant increase in sympathetic activity.[198] Fru semide causes renal vasodilatation which could activate intrarenal baroreceptors. In non-filtering kidneys, renal vasodilatation with papaverine blocks the effects of frusemide on renin secretion,[199] though renin release still occurs through macula densa mechanisms in filtering kidneys. Prostaglandins probably mediate frusemide-induced vasodilatation and also play a role in frusemide-stimulated renin release.[200,186] Frusemide releases renin from rat renal cortical slices but this does not appear to be inhibited by indomethacin.[201,202] In man, the natriuresis, hypotension, increase in renal blood flow, and increase in renin release caused by frusemide, may all be attenuated by indomethacin.[203,204] The early response is most profoundly affected,[205] while the later, volume-dependent, response is partially attenuated, perhaps because of the impaired diuresis.

Frusemide causes a rise in plasma arachidonic acid,[206] inhibits the conversion of prostaglandin E_2 to prostaglandin F_{2alpha}[208] and also probably enhances prostacyclin production.[208] However, loop diuretics increase renal intracapsular pressure, which may also stimulate prostaglandin production, though this can also be an effect of the prostaglandins themselves.

The increase in renin after frusemide is limited by the "negative feedback" of angiotensin II.[144] Angiotensin-converting enzyme inhibitors will release renin from this.

Osmotic diuretics

Osmotic diuretics appear to have a tri-phasic effect on renin release. Initial activation may be due to changes in juxtaglomerular cell volume;[209] renin suppression then occurs, probably as the sodium load increases at the macula densa,[210] then renin rises as the plasma volume contracts.

Thiazide diuretics

Prolonged treatment with thiazide diuretics leads to an increase in plasma renin,[211] which may be attenuated by propranolol and atenolol.[212,213] This is probably an effect of sodium and volume depletion.

Potassium-sparing diuretics

Amiloride increases plasma renin,[214] as does spironolactone,[215] despite increasing plasma potassium.

B) ANGIOTENSINOGEN

Otherwise known as renin substrate, it is a heterogeneously glycosylated $alpha_2$-globulin, with a molecular weight between 60,000-65,000 Daltons.[216] It is synthesised in the liver,[217] but more recent studies have indicated that mRNA is expressed in a variety of tissues,[218,219] suggesting that local angiotensin production may take place. Alterations in plasma angiotensinogen as well as renin concentrations may affect the rate of angiotensin I formation.[220] This reaction is the rate-limiting step in angiotensin II production. Pregnancy and oral contraceptives may elevate, and nephrotic syndrome depress, substrate concentrations.[221-224] Angiotensin II also stimulates increased hepatic synthesis of its own precursor, while other angiotensinogen fragments may inhibit production.[225,226] Severe parenchymal liver disease may reduce angiotensinogen production.[226]

C) ANGIOTENSIN I

Angiotensin I is largely devoid of activity, and it is always difficult to be sure that preparations are uncontaminated by some angiotensin II. Intrinsic effects on prostaglandins and adrenal catecholamines have been postulated.[227,228] Levels on the arterial side of the circulation are considerably lower than in the pulmonary artery due to conversion to angiotensin II in the pulmonary circulation.[229]

D) ANGIOTENSIN-CONVERTING ENZYME

This is identical to kininase II which degrades bradykinin but is not particularly specific for either. It can also hydrolyse enkephalins and the beta-chain of insulin. It is present in plasma but also widely distributed in the lungs, kidney and other tissues, largely bound to the endothelium.[230,231]

The angiotensin-converting enzyme is present in excess and is not the rate-limiting step in angiotensin II production.

E) ANGIOTENSIN II

This is the major active component of the renin-angiotensin cascade, and it has diverse effects. It has a half-life in the circulation of less than one minute.[232] It is largely degraded by enzymatic processes during transit through the capillary bed, and more slowly by angiotensinases in the circulation.[233,234] The effects of angiotensin II are generally considered to be mediated by a single receptor subtype, but in some tissues at least there is evidence for heterogeneity.[235,236]

Effects on blood pressure

Immediate Pressor Effect

Angiotensin II has very powerful direct arterial constricting effects.[237] This effect is receptor- mediated, and can be antagonised by saralasin, though it should be recognised that saralasin has partial agonist activity.[238,239]

Sustained high dosage results in tachyphylaxis.[240] The pressor effect is diminished by sodium depletion.[241] This may also represent receptor down-regulation, but could be due to a reduction in plasma volume, or a reduction in smooth muscle responsiveness.[242,243]

Slow Pressor Effect

If angiotensin II is infused over many days at doses which are initially subpressor, blood pressure will gradually rise.[244-246] This may be due to decreased vascular compliance, sympathetic activation, resetting of baroreceptors, enhanced aldosterone secretion, and sodium retention.[247-251]. It is difficult to reproduce this with other pressor agents.[246]

Venoconstriction

A direct effect of angiotensin II on limb veins is controversial, but only probably occurs at high concentrations which produce rapid tolerance.[252-256] However, it has been shown that local infusions of angiotensin II may facilitate reflex neurogenic venoconstriction that appear to be mediated through sympathetic presynaptic mechanisms.[252,257] Interestingly, although the direct venoconstrictor effects undergo rapid tachyphylaxis,[256] reflex venoconstriction does not appear to do so.[257]

Stimulation of Aldosterone Secretion

Angiotensin II increases plasma levels of aldosterone[258,259] by increasing adrenal secretion[260] and possibly by decreasing hepatic blood flow and hence aldosterone degradation.[261] However, a number of factors help modulate the stimulatory effects of angiotensin II, including dopamine and potassium.[259,262] In contrast to its pressor effects, sodium depletion enhances the ability of angiotensin II to stimulate aldosterone secretion, possibly by upregulating receptors.[263-266] During prolonged infusions, tolerance may appear, but this may be indirect due to potassium depletion[269] and is incomplete.

Inhibition of Corticotrophin Secretion

At high doses, infusion of angiotensin II can cause a rise in ACTH,[268] though the reverse has also been noted.[269] When administered into the cerebral ventricle it stimulates corticotrophin release, an effect also noted when applied to cultured anterior pituitary cells.[270,271] This may be part of a physiological local control system or be mediated through anti-diuretic hormone.[271]

Stimulation of Anti-diuretic Hormone Secretion

Concentrations of angiotensin II that are found in many patients with heart failure are capable of stimulating the production of anti-diuretic hormone.[272,273] The paraventricular nucleus contains a high quantity of angiotensin II receptors[274] and excitation at this level

appears responsible for anti-diuretic hormone release.[275] Central injections of angiotensin II can also stimulate oxytocin release.[276]

Sympathetic Transmission

There is evidence that angiotensin II may enhance sympathetic activity, both centrally and by peripheral pre- and post-synaptic mechanisms. Angiotensin II can produce a pressor response mediated through the area prostrema or periventricular nuclei (depending on species) which can be blocked by beta-adrenergic antagonists.[277-280] Tolerance does not develop to this pressor response and the effects may be seen with low dose carotid intra-arterial infusions.[281]

Acting on peripheral sympathetic fibres, angiotensin II may enhance tyrosine hydroxylase activity and hence noradrenaline synthesis.[282] Angiotensin II may also enhance noradrenaline release at sympathetic nerve terminals[283,284] and reduce re-uptake,[285] thereby increasing the concentration of noradrenaline in the synaptic junction. Angiotensin II may also potentiate the post-synaptic effects of noradrenaline.[287] However, responses to sympathetic stimulation are increased to a much greater degree than the responses to exogeneously administered noradrenaline.[287,288] Angiotensin II may also release catecholamines from the adrenal medulla.[289,290]

Parasympathetic Transmission

Angiotensin II has been shown to reduce vagal tone in animal experiments and in man, while captopril appears to enhance parasympathetic reflexes.[291-295] This is centrally mediated.[296]

Central Nervous System

Angiotensin II is not thought to cross the blood-brain barrier. However, some periventricular nuclei (eg, the subfornical organ, organum vasculosum laminae terminalis) and area postrema lie outside this and are thus susceptible to circulating angiotensin II.[297,298] All the components of the renin-angiotensin system, including angiotensin II receptors, are present within the brain itself.[299] Centrally administered angiotensin II also has a pressor effect.[300]

Direct Myocardial Effects

Direct postive inotropic effects of angiotensin II on the myocardium have been shown in both animal experiments and in man.[301-303] If the increase in blood pressure is prevented, there is also evidence of a direct chronotropic effect.[304, 305] The inotropic effect appears to be a calcium-mediated phenomenon.[305] However, the inotropic and chronotropic effects of angiotensin II are normally obscured by the responses to the increased arterial pressure.[304] In animal models angiotensin II administered to produce high "physiological" circulating levels may also induce focal myocardial cell necrosis.[306,307]

Effects on the Renal Circulation

Angiotensin II causes preferential constriction at the efferent arteriole, thus maintaining glomerular hydrostatic pressure, despite a reduction in the renal perfusion pressure during hypotension.[308-310] Increases in afferent arteriolar tone with angiotensin may occur in intact animals, but probably represent auto-regulation in response to the rise in perfusion pressure.[311] Angiotensin II may also cause a change in the intrarenal distribution of blood flow, diverting blood away from the outer cortical nephrons to the juxtamedullary nephrons.[312]

Glomerular Effects

Apart from hydrostatic pressure, glomerular filtration depends on the area available for filtration and the hydraulic conductivity of the glomerular wall. The product of the latter two is the ultrafiltration coefficient. Agents which reduce ultrafiltration coefficient cause glomerular contraction but have not been shown to alter glomerular ultrastructure.[313,314] Therefore, it has been assumed that changes in glomerular surface area are of more importance. Mesangial cells contain contractile myofilaments and possess receptors for angiotensin II, stimulation of which does appear to cause contraction.[315-319] Similar properties may exist in glomerular endothelial cells.[320] Angiotensin may therefore reduce glomerular filtration rate by causing mesangial cell contraction and

an increase in ultrafiltration coefficient. This will have the opposite effect on glomerular filtration rate to the effects of angiotensin II on the efferent arteriole.

Intrarenal Distribution of Blood Flow

It remains unclear what the importance of angiotensin II is to the distribution of intrarenal blood flow, although circumstantial evidence abounds. Firstly, superficial cortical nephrons contain more renin than the juxtamedullary[321] However, this gradient may be lost during sodium depletion and low renal perfusion pressure.[322,323] There is evidence that angiotensin II preferentially constricts cortical vessels.[324] Sodium deprivation in animals, which activates the renin- angiotensin system, diverts blood to the deeper, juxtamedullary nephrons.[325] In human heart failure, there is evidence of reduced cortical blood flow, which can be reversed by frusemide.[326] In rats and hypertensive man, there is some evidence that it can also be reversed by captopril.[327,328] Thus, angiotensin II diverts blood to the juxtamedullary nephrons which direct blood to the vasa vasorum of the long loops of Henle that reach down into the renal medulla. These changes in intrarenal blood flow may contribute to sodium retention in heart failure.[326]

Proximal Renal Tubule

Sodium is actively reabsorbed at this site by a variety of mechanisms. Sodium is exchanged for potassium at or near

the basement membrane, which leads to an electrochemical gradient for sodium reabsorption from the tubular lumen. This is greatly enhanced by a number of co- and counter-transport systems with other ions and solutes.[329,330] Water follows the osmotic gradient freely.

Angiotensin II causes the resistance at the efferent arteriole to increase, which produces a rise in glomerular filtration fraction. The oncotic pressure of plasma reaching the vasa vasora at the proximal tubule increases and the hydrostatic pressure falls. These peritubular capillary forces were long thought to contribute to proximal tubular reabsorption. However, both angiotensin II and sympathetic activation can lead to proximal tubular reabsorption in the absence of changes in oncotic or hydraulic pressure.[331-333] In- vitro experiments also suggest that noradrenaline and angiotensin II can stimulate proximal tubular sodium reabsorption directly.[334,355] However, at high concentrations angiotensin II may inhibit proximal tubular sodium reabsorption.[332,336]

Distal Tubule

The major effect of angiotensin II is mediated through aldosterone, which stimulates active sodium transport in exchange for sodium and potassium.[337] Aldosterone stimulates the production of a protein which mediates its effects on ion exchange. This leads to several hours delay in onset and offset of its effects.[338]

Stimulation of Drinking

Angiotensin II stimulates drinking in animals, an effect which is seen most powerfully when administered directly to the central nervous system.[267,269,339,340] There is some evidence that this may also be true in man.[341,342] Central administration of angiotensin II has also been reported to stimulate salt appetite.[343]

Internal Distribution of Electrolytes

Angiotensin II increases the infux of sodium into smooth muscle cells in exchange for potassium.[344,345] This may effect smooth muscle tone and vascular resistance.

Prostaglandins

Angiotensin II may stimulate the renal production of prostaglandins of the E series.[346,347] This effect of angiotensin II may be organ-specific since it has been shown not to occur at other sites.[348] The renal release of prostacyclin and prostaglandin E_2 tend to occur in situations which also provoke renin release,[349,351] and their production leads to afferent arteriolar vasodilatation.[352]

Indomethacin can attenuate the renal vasodilator effects of converting enzyme inhibition[353,354] Some studies have suggested that converting enzyme inhibitors may actually stimulate prostaglandin synthesis, though this may be a bradykinin-dependent pathway.[355,356]

Renin

Angiotensin II appears to directly inhibit renin production (vide supra).

Biochemical Mediation of the Effects of Angiotensin II

Occupation the angiotensin II receptor stimulates the hydrolysis of the phosphatidylinositol 4,5-biphosphate and inhibits the production of cyclic AMP (adenosine monophosphate).[357,358] In turn this increases intracellular free calcium, enhancing contraction.[359]

Angiotensin II as a Growth Factor

Angiotensin II has recently been implicated as a proto-oncogene. Thus, angiotensin II may induce hypertrophy of cardiac and vascular myocytes.[360,361]

Tissue Renin-Angiotensin Systems

The capacity to produce renin and angiotensinogen is of course present in the DNA of all cells. Messenger RNA for renin and angiotensinogen has been found in many tissues, indicating likely local synthesis,[362,363] though a physiological action is not clearly established. Cells also appear to have the ability to take up components of the system from other cells and the circulation. Locally synthesised angiotensin II may have effects on the cell in which it was synthesised (autocrine effect) or on adjacent cells (paracrine effect). However, nephrectomy causes a

rapid disappearance of renin activity from vascular tissues, suggesting that local synthesis of renin is of lesser importance,[364] though plasma inactive renin is little affected.

F) ALDOSTERONE

Aldosterone secretion is stimulated by angiotensin II, corticotrophin and a fall in plasma potassium.[258-266, 365-368] Aldosterone secretion is inhibited by atrial natriuretic peptide and dopamine,[262,369,370] the apparent degree of inhibition increasing as angiotensin II stimulation increases. This competitive action does not seem to be mediated through angiotensin II receptors. Sodium depletion and potassium loading enhance the sensitivity of aldosterone secretion to angiotensin II,[258,259] while aldosterone secretion may be controlled, at least in part, by locally formed angiotensin II.[371]

A 25% increase in plasma aldosterone may occur with an infusion of as little as 10 mmol potassium,[366] an amount which does not alter plasma potassium concentration. Aldosterone also varies as the dietary intake of potassium.[365] The effects of potassium on aldosterone secretion probably out-weigh those of angiotensin II.[367] Dietary sodium restriction stimulates renin-angiotensin activity, and thereby aldosterone. Only large changes in plasma sodium concentration appear to affect aldosterone secretion directly.[372]

Corticotrophin is a powerful aldosterone secretagogue but tachyphylaxis to its effects occur within 6 hours.[368] Anti-diuretic hormone has also been observed to stimulate aldosterone secretion, at least in-vitro, through stimulation of V_2 receptors, though again tachyphylaxis is seen.[373] The granulosa cells are richly innervated, and beta-receptor stimulation could also enhance steroid synthesis.[374]

Atrial natriuretic peptide inhibits aldosterone secretion in response to the above stimuli in animals and in-vitro. In man, infusions of atrial natriuretic peptide also cause a fall in aldosterone, but this may not be observed if baseline levels are low.[370]

Dopamine probably inhibits aldosterone secretion through D-2-receptors.[262,375]. Bromocripitine can attenuate frusemide-induced aldosterone release, while metoclopramide raises plasma levels of aldosterone.[376,377]

Actions

Aldosterone stimulates sodium uptake and potassium loss in the renal tubule, and the salivary and sweat glands[378] The site of action is the distal tubule and collecting duct, where sodium uptake is coupled to potassium and hydrogen ion excretion.[378] With continued administration, normal subjects will eventually "escape" from the sodium-retaining

effects of aldosterone. This is largely due to a reduction in proximal tubular reabsorption and may be an effect of atrial natriuretic peptide.[379] Patients with heart failure do not "escape" from the sodium-retaining effects of aldosterone.[380]

SUMMARY

There are therefore many reasons for the renin-angiotensin-aldosterone system to be stimulated in patients with heart failure. Many of the actions of angiotensin II and aldosterone could be deleterious. However, angiotensin II and aldosterone may have a central role in supporting the blood pressure in heart failure while angiotensin II may help maintain glomerular filtration rate. Therefore, interference with these systems cannot automatically be assumed to be beneficial.

CHAPTER 3: ANIMAL MODELS OF NEUROENDOCRINE ACTIVATION IN HEART FAILURE

Probably the first "model" investigating neuroendocrine activation in heart failure was in man, when an increased concentration of renin was noted in renal vein blood of patients with chronic heart failure.[381]

Few studies of neuroendocrine function exist on animals with heart failure due to left ventricular damage, and thus it is difficult to equate animal models with human disease. Ertl and others have suggested that ACE inhibitors improve ventricular function and reduce ventricular arrhythmias after myocardial infarction in animal models, though some have speculated that this may be a specific property of the captopril molecule rather than an effect of ACE inhibition.[382,383,384] The effects of ACE inhibitors on survival have also been studied in rats with left ventricular dysfunction due to myocardial infarction.[385] However, the neuroendocrine effects of such cardiac insults have been studied only rarely, and often indirectly,[386,387] and do not generally provide sufficient information to understand, in detail, neuroendocrine activation under such circumstances.

A low cardiac output has been induced in animal models by vena caval constriction, but in this model atrial pressure is reduced, unlike common forms of human disease. Pulmonary banding and tricuspid avulsion results in a low cardiac output and raised right atrial pressure, but the left

atrium and ventricle are only secondarily affected. High output failure has been induced by arteriovenous fistulae, but again these models do not closely parallel the common human condition. Riegger developed an interesting dog model of heart failure by rapid ventricular pacing, but, again, this is not an accurate simulation of common human forms of heart failure. Nonetheless, valuable insights and analogies may be drawn from these less representative models from which we have a large amount of data.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Despite the fact that renin[381] and angiotensin II[388] were shown to be elevated in early studies of patients with heart failure, early animal studies failed to show a consistent increase in renin or aldosterone, despite marked sodium retention.[389-392] Transient increases in renin and aldosterone were noted after tricuspid avulsion or vena cava constriction, which were dismissed by some and studied by others.[389,392]

When normal humans and dogs are administered aldosterone, they retain water only transiently.[393,394] After retaining sodium for a few days they "escape" from the sodium-retaining properties of the steroid. In a series of experiments, Davis et al, using a low cardiac output (vena cava constriction) dog model, showed that dogs with heart failure did not undergo "escape" from a mineralocorticoid.[395,396] This had previously been shown in

man[397] This was not due to increased renal vein pressure and was unaffected by hypophysectomy, adrenalectomy and renal denervation. Davis was also able to induce the same effect in a high output model with an arteriovenous shunt[398] and showed that sodium retention varied according to the administered dose of steroid and noted de Wardener's suggestion that a natriuretic factor may be at play.[399] We now know that this model of heart failure, by reducing atrial stretch, may well reduce secretion of atrial natriuretic peptide, thus enhancing the sodium-retaining effects of aldosterone. An increase in atrial natriuretic peptide may well have been the much sought after mechanism of the "escape" phenomenon.[400]

In dogs with an arteriovenous fistula, which usually only develop features of heart failure when given additional aldosterone, it was noted that angiotensin II could induce further secretion of aldosterone, heart failure and ascites.[401] This could be prevented by adrenalectomy. These investigators also noted a reduced pressor response to angiotensin II, though whether this was due to contraction of plasma volume, prior receptor occupation or down-regulation, or a fall in cardiac output, was not investigated.

Despite Davis' claims that an effective excess of aldosterone was necessary for the production of the signs of congestive heart failure, this was not confirmed by the

advent of specific aldosterone antagonists. In human studies, spironolactone was found to elicit a diuresis in only 40% of patients. Moreover, the diuresis had a poor relationship to the measured level of aldosterone.[402]

Additional studies of inferior and superior vena cava constriction around this time demonstrated that the rise in renal venous pressure was not the cause of sodium retention, but did show that sodium retention could be blocked by hexamethonium or phenoxybenzamine.[403,404]

In one of the most elegant experiments to date, Watkins et al showed that heart failure induced either by inferior vena cava or pulmonary artery constriction was followed by a fall in arterial pressure, intense activation of renin and aldosterone and marked sodium retention.[405] After one or two days, plasma volume expansion became obvious, arterial pressure rose, urinary sodium returned to control, and activity of the renin-angiotensin-aldosterone system waned, at least in dogs subjected to moderate constriction. Initially, single doses of an ACE inhibitor produced further marked falls in arterial pressure. If these dogs received further single doses of an ACE inhibitor on subsequent days the resultant fall in pressure diminished progressively and was lost after 10 days. At this time, renin had returned to normal.

In dogs subjected to more severe constriction, the fall in

arterial pressure was greater, activation of renin and aldosterone persisted, sodium retention was progressive and plasma volume was not expanded. Prolonged treatment with an ACE inhibitor prevented the rise in aldosterone, but exacerbated the fall in arterial pressure, did not reverse sodium retention and prevented mildly affected dogs from regaining haemodynamic equilibrium. A similar important role for angiotensin II in maintaining blood pressure under these circumstances has been suggested from studies with saralasin.

In the studies by Watkins et al, they also noted that the major cause of water "retention" was increased consumption. They attributed this to a dipsogenic effect of angiotensin II, though they did not comment if thirst was affected in the dogs treated with an ACE inhibitor. Sodium retention, rather than angiotensin II, could have accounted for the increase in thirst. They also noted that the increase in renin was greater in dogs put into heart failure by vena cava constriction compared to pulmonary artery constriction. Though this could be explained by low atrial pressure stimulating vagal afferents and hence increased sympathetic outflow to the kidney, an increase in atrial natriuretic peptide with right atrial distension leading to inhibition of renin release is equally plausible.

In contrast to the above, Freeman et al, using a similar animal model, noted that ACE inhibition resulted in a

suppression of aldosterone and a natriuresis.[406] However, the data are not so inconsistent on more detailed examination. Only those dogs that had a well maintained arterial pressure and glomerular filtration rate during angiotensin-converting enzyme inhibition had a marked natriuresis. Sodium retention occurred in those dogs where arterial pressure fell to any great extent after an ACE inhibitor.

Riegger et al have used rapid ventricular pacing as a model of heart failure.[407] In this model, induction of heart failure is accompanied by activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, and anti-diuretic hormone (ADH). Levels of ADH were inappropriately elevated in relation to plasma osmolality. In a subsequent series of experiments, inhibiting each of these systems using captopril, prazosin or an anti-diuretic hormone (V_1) receptor antagonist, they showed that the latter had little effect on the elevated peripheral vascular resistance of heart failure.[408,409] Prazosin had a transitory effect only which may have been reversed by activation of renin. Only captopril produced sustained beneficial haemodynamic effects. They also suggested that captopril prevented fluid retention. However, the effects of ACE inhibition on sodium excretion in animal models is highly variable. One explanation may be variations in sodium loading. It has been shown in rats that ACE inhibitors actually induce sodium retention in salt-deplete

animals and the reverse in sodium- loaded.[410] Animals with heart failure may be more likely to behave as sodium-deplete, or, expressed in another way, have increased renal sodium avidity. Studies with renin inhibitors suggest that they too may have beneficial haemodynamic effects in heart failure but also fail to increase sodium excretion.[411]

Activation of the renin-angiotensin system may precipitate worsening heart failure and hence further activation of neuroendocrine systems in at least 2 ways. Firstly, the increase in vascular tone may cause a further increase in atrial pressure and a decline in cardiac output. More subtly, angiotensin II may cause focal myocardial necrosis in supra-physiological doses, leading to deterioration in intrinsic myocardial function

ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) is also elevated in heart failure, with increased atrial turnover and depleted atrial stores.[387] That the natriuretic response to ANP is impaired in heart failure is well described.[412,413] In animal models, restoration of renal artery perfusion pressure has been shown to restore the natriuretic response,[414] while the effects of angiotensin II, aldosterone and sympathetic nervous system activation may all impair ANP's natriuretic effects.[415] Administration of anti-ANP antibodies in animals with heart failure elicits further sodium retention,

suggesting that the increased levels of ANP in heart failure are not inert.[416]Administration of an atriopeptidase inhibitor to elevate plasma levels of ANP are also associated with a diuresis.[417] There are reports that ANP receptors may be reduced in heart failure, at least on platelets.[418]

ANTI-DIURETIC HORMONE

Further studies on hypophysectomy before and after the induction of heart failure suggested that increases in plasma levels of ADH had little impact on sodium and water retention in heart failure.[419,420] Some animal models have suggested an important role for ADH-induced vasoconstriction, which may be enhanced by the baroreceptor impairment which occurs in heart failure.[421,422] However, marked haemodynamic effects from ADH-V_1 receptor inhibition are uncommon.[423]

SYMPATHETIC NERVOUS SYSTEM

In addition to an increase in circulating catecholamines which reflect increased sympathetic nerve traffic, cardiac stores of noradrenaline are reduced in animal models of heart failure.[424] There appears to be a reduction in cardiac synthetic capacity and decreased neuronal re-uptake of noradrenaline.[425,426] Reduction in activity of tyrosine hydroxylase activity, the rate- limiting step in noradrenaline synthesis, has been noted.[427,428] It is now generally agreed that cardiac $beta_1$ receptors are

down-regulated in heart failure, leading to a reduction in sensitivity to adrenergic stimuli,[429-431] while $beta_2$ and alpha-receptors are relatively less affected.

Increased cardiac sympathetic activity may be beneficial initially, increasing the force of cardiac contraction and heart rate. However, sustained high levels of sympathetic activity may lead to focal myocardial necrosis[432,433] and/or progressive ventricular dysfunction and arrhythmias. Increased peripheral sympathetic activity leads to increased arterial and venous tone and renal sodium retention.[434-441]

Inhibition of $alpha_1$ receptor-mediated increases in vascular tone in animal models leads to transient beneficial haemodynamic effects only.[407,408] The reasons for this are not clear. As non-specific $alpha_2$ receptor blockade may also have taken place, this could have led to heightened sympathetic activity and a reversal of the initial beneficial effect. Alternatively, Zelis has suggested that heightened peripheral sympathetic activity may actually have a beneficial effect in heart failure, directing blood flow during exercise to the most metabolically active muscle fibres.[442,443]

Activation of the renin-angiotensin system commonly occurs during prazosin therapy and may be responsible for haemodynamic tolerance, though such activation could also

represent a response to overall haemodynamic deterioration or to heightened renal sympathetic activity.

CONCLUSIONS

Animal models offer valuable insights into the dynamic responses of neuroendocrine systems in heart failure. These models must be treated with caution due to the time course and character of the haemodynamic perturbation. Important differences between species may occur, and this is especially likely when extrapolating to humans, the only bipeds so far studied, whose cardiovascular system has been specifically adapted for the upright posture.

CHAPTER 4: NEUROENDOCRINE ACTIVATION IN HUMAN HEART FAILURE

Relatively few studies exist of the development of heart failure in man. McAlpine et al[444] demonstrated an increase in activation of the sympathetic nervous and renin-angiotensin systems and arginine vasopressin after myocardial infarction. Those patients who went on to develop clinical evidence of heart failure demonstrated sustained neuroendocrine activation. In contrast, in those patients who recovered without developing evidence of heart failure neuroendocrine activation declined.

In contrast, Bayliss et al[445] studied patients with untreated compensated heart failure during rest and exercise, demonstrating excessive activation of the sympathetic nervous system but that the renin- angiotensin system appeared suppressed. However, it should be noted that there were no healthy controls in this study and the authors only compared their results with a reference range. Milder degrees of neuroendocrine activation therefore may have been missed. However, in a series of patients presenting with acute left ventricular failure, Broqvist et al[446] suggested again that whereas the sympathetic nervous system was activated, there was little evidence of activity within the renin-angiotensin system. They also demonstrated that plasma levels of atrial natriuretic peptide were high and fell with diuretic therapy. However, it should be noted that the patients presenting with acute left ventricular

failure in this study appeared to be hypertensive. A series of case reports[447,448] has suggested that the arterial pressure may have a major impact upon renin-angiotensin system activation in untreated heart failure. This may explain the heterogeneity of neuroendocrine activation in untreated heart failure.[449,450]

These findings are all consistent with animal models of heart failure in which initial activation of the sympathetic nervous and renin-angiotensin systems results in fluid retention and vasoconstriction. Arterial pressure returns to normal or may even be raised when blood volume is expanded, resulting in a waning of neuroendocrine activation. However, if the cardiac insult is severe and acute, then failure to maintain stroke output and pressure may lead to shock; or the very high filling pressure resulting from failure of ventricular emptying may result in pulmonary oedema, even though it may be required to maintain cardiac output. Under these circumstances, when haemodynamic equilibrium cannot be achieved, neuroendocrine activation may be intense. The majority of patients with chronic heart failure are already receiving diuretics which maintain activation of the neuroendocrine systems.[446,451] Conversely, diuretics may also reduce the intrinsic neuroendocrine activation of acute heart failure.[446,449] This is probably due to withdrawal of acute sympathetic activation with the resolution of pulmonary oedema. A reduction in atrial pressure will also cause a decline in

plasma atrial natriuretic peptide.[452]

While recent interest has concentrated on vasoconstrictor mechanisms in heart failure, the failure of vasodilator mechanisms such as atrial natriuretic peptide, bradykinin, and the vasodilator prostaglandins may be important.[453] Patients with heart failure demonstrate simultaneous activation of both vasoconstrictor and vasodilator systems; plasma levels of noradrenaline, renin, angiotensin II, aldosterone, arginine vasopressin and atrial natriuretic peptide all being elevated, in contrast to the reciprocal relationships seen in normal subjects.[454]

Neuroendocrine activation becomes more intense as the diuretic dose is increased. Exercise causes further stimulation of the sympathetic nervous system[455-457] and renin-angiotensin system,[458] and arginine vasopressin and atrial natriuretic peptide.[459] However, there is marked individual variation in the intensity of activation. Low serum sodium, potassium and arterial pressure levels are more accurate clinical markers of intense neuroendocrine activation than symptom class or level of ventricular dysfunction.[460]

Plasma concentrations of renin, angiotensin II, noradrenaline and atrial natriuretic peptide are inversely related to prognosis.[461,462] High levels of catecholamines and angiotensin II may be directly cardiotoxic and add to a

downward spiral of increasing vascular resistance, neuroendocrine activation and deteriorating haemodynamic function.

However, it remains uncertain whether neuroendocrine activation itself makes a contribution to increasing mortality or is just a marker of severity. The demonstration that low levels of renin-angiotensin system activity with high sympathetic activity may be exchanged for the converse by diuretics illustrates the absence of any simple relation between neuroendocrine activation and prognosis. Though diuretics are central to the management of severe heart failure, it is possible that they may adversely affect prognosis in mild heart failure because of unfavourable changes in haemodynamic, metabolic or neuroendocrine factors. This is especially likely if excessive doses result in reduction in body fluid compartments below normal.

CHAPTER 5: CARDIOVASCULAR ADAPTATIONS IN HEART FAILURE

PRELOAD

Preload, the resting myocardial tension, is determined by the degree of actin/myosin overlap of the contractile units of the myocytes. Due to slippage between myocytes in chronically distended ventricles, actin/myosin overlap may be similar in diseased and normal hearts [463] so it cannot easily be predicted where the patient "is" on the Frank-Starling curve. The effects of a reduction in preload are also difficult to predict. A small increase in venous capacity may lead to an effective reduction in ventricular volume without affecting cardiac output. Larger falls in volume will result in a fall in output. It is likely that patients die before reaching the descending limb of the Starling curve and therefore unlikely that reduction in preload alone will ever cause a rise in cardiac output. Reducing blood volume by venesection or diuresis is effective in lowering ventricular filling pressures [464,465] but since many of the haemodynamic, autonomic and endocrine consequences of heart failure appear similar to those of blood loss, further stimulation of these adaptive mechanisms appears undesirable.

AFTERLOAD

Afterload, the resistance which the ventricle has to overcome ion order to eject its contents, depends on the radius of the chamber, the energy required to deform the

myocardium, the systolic pressure that it generates and the aortic impedance (a synthesis of arterial compliance and arteriolar resistance).[465] The normal, but not the failing, ventricle, compensates for rises in afterload by an increase in contractile force so that the stroke output remains unchanged. This law of the heart, less well known than Starling's, was described by Sarnoff, and is equally important.[466] It follows that reduction of afterload by arteriolar dilators allows the ejection fraction and stroke output to rise, with little effect on filling pressures unless more complete ventricular emptying reduces cardiac volumes so that both preload and afterload fall. Diuretics may also reduce afterload, either by reducing external arterial compression by oedema [467] or by altering the composition of the vessel wall (ie reducing sodium content).[468]

CARDIAC ADAPTATION TO HEART FAILURE

Four basic processes are recognised by which the heart may attempt to compensate for declining function. Myocardial contractility may be increased by activating intrinsic myocardial mechanisms according to the Frank- Starling principle or by exogenous neuroendocrine factors. In addition, cardiac output may be maintained by increasing heart rate, and myocardial hypertrophy may occur in order to cope with the altered loading conditions of the ventricles.

The Frank-Starling Principle

Both atrial and ventricular muscles behave according to Starling's law that "The mechanical energy set free on passage from the resting to the contracted state is a function of the length of the muscle fibre".[469]

In the normal heart, an increase in venous return on exercise or due to a rise in intravascular volume distends the cardiac chambers (ie increases preload). A concomitant change in actin-myosin overlap enhances the myocardial contractile state, stroke volume rises and diastolic chamber volume tends to return to normal. Sarnoff and Mitchell[466] examined ventricular stroke work over a range of end-diastolic pressures and termed the resulting relation the Ventricular Function Curve. Movement along a single curve represents operation of the Frank-Starling principle. Displacement of the curve reflects a change in inotropic state of the ventricle.

In heart failure, the Frank-Starling principle still operates but the curve on which the heart functions has changed, ie, there is a change in the inotropic state of the myocardium. This has its sub-cellular correlate. Actin-myosin overlap and sarcomere length seem to be the same in a chronically dilated and normal heart. In the canine left ventricle, sarcomere length is similar, with end-diastolic pressures from normal up to 60 mm Hg. Further rises in preload up to 100 mm Hg reduced developed pressure

by only 7.5%[463,470] However, length/tension relationships are not the same as pressure/volume relationships. According to Laplace's law, afterload also increases as the cardiac chamber dilates and if there is a decreased cardiac reserve, reduced myocardial wall shortening in systole will occur. The development of mitral regurgitation during ventricular dilation may also decrease forward stroke volume and result in an apparent depression of ven tricular performance as preload is elevated. These two mechanisms probably account for the observed depression of cardiac function at high preloads. It is doubtful if the human myocardium ever reaches the descending limb of the Frank-Starling curve. However, chronic ventricular dilatation presumably puts the myocyte at a disadvantage whenever a further acute increase in loading occurs, as during exercise. In the management of heart failure with venodilators, the Frank-Starling principle could have more adverse consequences: reduced preload may cause an apparent decline in cardiac contractility. However, a reduction in end-diastolic volume will reduce afterload according to Laplace's law. Of course, the reduction in contractility due to the reduction in end- diastolic sarcomere length may only be temporary, just as ventricular distension leads to myocyte slippage, rather than sarcomere lengthening in the chronically dilated heart, reduction of dilatation may reverse this process.

In summary, the Frank-Starling principle seems designed to

deal with short term events only, ie, exercise, acute volume loading, etc. However, there are advantages in reducing ventricular filling pressure and therefore atrial and intra-pulmonary pressures. Reducing chamber size will also reduce ventricular afterload.

Extrinsic Factors affecting Myocardial Contractility

As we have already observed, the Frank-Starling principle is one mechanism by which myocardial contractility can be altered to cope with short term changes in volume loading. An alternative mechanism of increasing contractility to maintain cardiac output and ventricular filling pressures is to introduce an inotropic substance. Chief among the naturally occurring mechanisms must be cellular handling of calcium ions[471-473] and the sympathetic nervous system,[474-475] though it should be noted that the latter may mediate its effect through changes in cytosolic calcium. There may be lesser contributions from glucagon, angiotensin II, histamine and sodium.[476-480]

Intracellular calcium ions and adenosine triphosphate may well be the final determinates of the contractile state of the myocyte, and are also essential for relaxation. Though extra-cellular calcium ions can have a pronounced inotropic effect, perhaps most clearly seen in man when electromechanical disassociation may result from the intravenous use of verapamil,[481] cellular calcium ion overload could eventually result in cell death.[482]

Hypophosphotaemic cardiomyopathy is poorly understood but may be due to impairment of glycolytic pathways,[483] or changes in calcium ion flux across cell membranes.[484]

A rise in sympathetic nervous system activity appears an almost constant accompaniment to cardiovascular stress. In untreated heart failure a rise in plasma noradrenaline has been shown, even prior to the introduction of diuretic therapy. In acutely decompensated heart failure, tachycardia, resulting from this increase in sympathetic nerve activity is common; in chronic heart failure sympathetic nervous system activity and tachycardia may be less marked. This may be due in part to impaired intracardiac conduction but changes in receptor density or function and/or defects in myocardial catecholamine synthesis may occur. Bristow and others[485] have shown evidence of beta-receptor down- regulation on the myocardium. Down-regulation of $beta_1$- receptors appears more pronounced than for $beta_2$. Although there are many technical explanations for down-regulation of beta receptors, the observation that in-vitor myocardial tissue also demonstrates reduced cardiac sympathetic responsiveness strongly suggests a functional as well as a numerical reduction in receptor sites. However, evidence also exists for a reduction in activity of such enzymes as tyrosine hydroxylase, the rate-limiting step in noradrenaline synthesis in sympathetic nerve terminals.

Although several authors have indicated that the concentration of contractile proteins within the myocyte may be reduced in heart failure, there is no universal agreement on this subject. Indeed, some have argued that individual myocyte contractile function in heart failure is normal, and that no intracellular defect to receptor-mediated stimuli exists.

Some of the recent evidence suggesting that individual myocyte function in heart failure is normal may seem surprising. However, a defect in the collagen matrix in which the myocytes exist may be the fundamental problem in such conditions as dilated cardiomyopathy. If the collagen matrix becomes rigid, then it would become difficult for myocytes to either contract or relax. There are limitations to the interpretation of the data; in particular, studies on isolated myocytes are technically complicated. The myocytes that survive the harvesting process may well be the "fittest" and cells are generally studied in unloaded conditions. It is also possible that myocyte function is rapidly restored once the cell is removed from its adverse environment.

The Heart Rate

The most obvious means by which the heart compensates with increased metabolic demand (ie exercise) is by increasing the heart rate. The rise in stroke volume during stress makes relatively little contribution to the rise in cardiac

output. In heart failure the rise in sympathetic drive and fall in parasympathetic activity results in a rise in resting heart rate to help maintain cardiac output, at least in the absence of conducting system disease. This phenomenon is much more obvious in acute rather than chronic heart failure, and may be related to receptor down-regulation or a depletion in cardiac noradrenaline stores due to a defect in synthesis, as discussed above. Digoxin therapy may also further suppress the heart rate.

There would appear to be no intrinsic harm in raising heart rate to maintain cardiac output but if myocardial compliance is depressed and ventricular distensibility reduced, ventricular filling may be impaired and cardiac output compromised. Additionally, most of the coronary blood flow occurs in diastole: in heart failure, where myocardial oxyen supply may be already precarious,[488] this may further derange myocyte metabolism and cardiac contractility.

Myocardial Hypertrophy

In heart failure, afterload is increased both due a rise in systemic vascular resistance and due to the dilatation of the cardiac chambers, according to Laplace's law. The decline in cardiac output is generally proportionally greater than the rise in systemic vascular resistance, hence, patients with heart failure, as a population, have a lower blood pressure than subjects without heart failure

The stimulus to left ventricular hypertrophy in heart failure is, as yet, unknown, but might include alterations in sympathetic nerve activity, angiotensin II, local tissue messengers, or change in cell function as a direct consequence of a change in loading conditions.[489,490] In patients with hypertension there is some evidence that agents that block the sympathetic nervous system or angiotensin II production may cause more regression of left ventricular hypertrophy than agents such as hydralazine that do not.[491-493] This suggests that mechanical stress alone is not the sole determinant of left ventricular hypertrophy. Left ventricular hypertrophy tends to normalise the stress imposed on each sarcomere in diastole and systole as cardiac volume rises. Of course, this normalisation of wall stress requires more energy to deform the myocardium itself and may reduce diastolic filling and also systolic function. This adaptive process is therefore not a perfect answer to the change in loading conditions and could be conceived as contributing to the problem in some patients.

REGIONAL BLOOD FLOW

The increase in systemic vascular resistance is not uniform among the vascular beds. Renal, skin and splanchnic vascular resistance are often markedly increased while cerebral and coronary vascular resistance are little altered. Skeletal muscle blood flow is only slightly

reduced at rest until heart failure is far advanced, but fails to rise normally on exercise even at an early stage. Interventions that increase cardiac output may fail to increase the blood supply to those organs where it is required. Even if the blood flow to an organ does increase, it may still be nutritionally ineffective if it bypasses metabolically active areas.

CUTANEOUS BLOOD FLOW IN HEART FAILURE

Cutaneous blood flow is reduced at rest only in very severe heart failure [494,495]. In mild-to-moderate congestive cardiac failure, cutaneous blood flow is not significantly reduced at rest. However, during exercise, sympathetically-mediated cutaneous vasoconstriction becomes marked,[495] and is sustained throughout the entire period of exercise. In addition, as the absolute amount of work done during exercise may be less, the thermal stress on the cutaneous circulation is reduced.

THE SPLANCHNIC CIRCULATION

In severe cardiac failure the splanchnic blood flow is often severely reduced. In milder heart failure splanchnic blood flow may be reduced only during exercise.[494] The splanchnic blood flow seems more under the influence of the sympathetic nervous system, with little contribution from angiotensin II.[496,497]

CEREBRAL BLOOD FLOW

In heart failure cerebral blood flow appears to be decreased.[498,499] Although studies in animals and man have shown that cerebral circulation can auto-regulate despite a wide variation in perfusion pressure,[500] in heart failure the cerebral blood flow seems unable to compensate for the fall in perfusion pressure. This may be due to increased sympathetic activity.[501,502] There is as yet no direct evidence that angiotensin II or anti-diuretic hormone influence cerebral blood flow.

In patients with heart failure, in contrast to normal subjects, cerebral blood flow probably declines during exercise.

RENAL BLOOD FLOW

As cardiac output falls, so too does renal blood flow.[503-505] In early heart failure this is evident only during exercise[506] while at rest, renal blood flow, glomerular filtration rate, and filtration fraction are normal. With worsening cardiac function, the haemodynamics become relatively fixed. Renal blood flow may be further upset by arrhythmias commonly seen in this condition.[507] In experimental heart failure in animals there is also redistribution of blood flow, with a relative reduction of cortical, compared to medullary, flow. This results in diversion of blood to the juxta- medullary nephrons, whose loops of Henle and associated vasorecta descend deep into

the medulla and are re sponsible for counter-current exchange, and may be important in maintaining the production of a concentrated urea-rich but sodium-poor urine that is characteristic of heart failure. Such data as exists suggest that re-distribution of renal blood flow in favour of the medulla also occurs in heart failure in humans, though most studies of renal function have been carried out on patients treated with diuretics.[508-511]

In addition to the fall of cardiac output, other factors affecting renal blood flow in heart failure include increased sympathetic nerve activity, leading to afferent arteriolar constriction, and a fall in renal blood flow.[512,513] In the early stages of heart failure, the fall in renal blood flow may not be accompanied by a corresponding fall in glomerular filtration rate because glomerular hydrostatic pressure is maintained by efferent arteriolar constriction, thought to be mediated by angiotensin II.[514,516] This leads to an increased filtration fraction, though probably a further reduction in renal blood flow. Even greater levels of angiotensin II cause, in addition, afferent arteriolar constriction, leading to a further fall in renal blood flow and glomerular filtration rate.

SKELETAL MUSCLE BLOOD FLOW

Skeletal muscle blood flow is altered little at rest in patients with heart failure until the evidence of cardiac dysfunction is severe.[517] However, exercise- induced vasodilatation is markedly impaired, even in milder degrees of heart failure.[518-521] Additionally, blood flow to the non-exercising limb is considerably reduced, suggesting generalised neurendocrine activation with vasoconstriction limited in the exercising limb by metabolic factors.

When patients with congestive heart failure exercise, frequently the blood pressure shows little or no increase, and occasionally exercise-induced hypotension results.[521] If the resistance vessels in active skeletal muscle dilated normally and there were not excessive arteriolar constriction elsewhere, syncope would occur more commonly during exercise, assuming that the cardiac output could not respond adequately.

The origin of the increased vascular stiffness has not yet been fully elucidated. Although sympathetic activity is heightened during exercise, nerve blockade of the forearm or intra-arterial injections of phentolamine into the exercising limb fail to normalise arteriolar responses.[520] Infusion of noradrenaline to produce circulating levels normally seen during exercise in patients with heart failure did not reduce the reactive hyperaemia response. However, infusion of noradrenaline in this way is certainly

not physiological and may represent only a small fraction of the sympathetic activity mediated physiologically through nerve terminals. However, these studies have really only considered the hyperaemic response to a maximal metabolic stimulation, whereas alpha-adrenergic tone probably only plays a regulatory role during sub-maximal stimulation. It generally appears that no vasodilator so far tested has been able to substantially alter the reactive hyperaemia during limb ischaemia or exercise. One factor that might contribute to the arteriolar stiffness seen in congestive heart failure is an increased sodium and water content of the resistance vessels.[522,523] Initially it was noted that after diuresis there was some restoration of the reactive hyperaemia response towards normal. It was also demonstrated that the sodium content of large and small arteries is increased. When mineralocorticoids and salt are administered to normal volunteers, this may also attenuate the peak reactive hyperaemic response.[524] Another explanation for the altered hyperaemia after ischaemia or exercise is increased tissue pressure in patients with heart failure.[525] Thus, vasodilators per se may have a limited role in improving skeletal muscle blood flow during exercise. Diuretics or other substances which are able to alter the sodium-potassium homeostasis may be more effective. Although it has been demonstrated that $alpha_1$-adrenergic receptor antagonists may increase skeletal muscle blood flow during sub- maximal exercise, it has also been noted that the oxygen consumption of the limb does not

undergo corresponding improvement. This suggests that the increased skeletal muscle blood flow is diverted away from the metabolically active muscle.

Changes in skeletal muscle blood flow during exercise in heart failure are further complicated by the abnormalities of skeletal muscle mass and function. Thus, the reduction in limb blood flow could reflect a reduction in oxygen requirements of the exercising limb. However, during exercise femoral venous oxygen saturation is uniformly lower in patients with heart failure, suggesting that decreased oxygen requirement is not the cause of reduced exercise limb blood flow. Moreover, lactate production during exercise is greater in patients with heart failure,[526] suggesting that the metabolic stimulus during exercise to reduce arterial dilatation is greater in heart failure subjects.[527-529]

SUMMARY

The cardiovascular adaptations to chronic heart failure are complex. They involve not only the heart but also the peripheral circulation. These are closely integrated, but the relationship between the two is markedly different during exercise.

Although heart failure is characterised by markedly elevated vascular resistance, this varies considerably among the regional circulations. Non-specific

vasodilatation may reduce vascular resistance. However, if this diverts blood from the renal circulation at rest, or the cerebral or skeletal muscle circulations during exercise, it could be deleterious.

CHAPTER 6: VASCULAR TONE IN HEART FAILURE: THE NEUROENDOCRINE-THERAPEUTIC INTERFACE

INTRODUCTION

Impaired cardiac function is of course the primary problem in heart failure, but it is also the primary stimulus to activation of several integrated neuroendocrine systems. This results not only in a general increase in vascular tone but also changes in regional arterial resistance. Activation of these neuroendocrine systems at first appears to have important beneficial effects for the failing circulation, maintaining cardiac output, blood pressure and blood flow to essential organs. However, prolonged or extreme neuroendocrine activation may prove deleterious.

The advent of effective diuretics had tremendous impact on the management of patients with heart failure, but then, in the absence of a cure for the primary problem, thoughts turned to altering vascular tone and it soon became apparent that the body countered this with heightened autonomic and humoral activity. The success of angiotensin-converting enzyme inhibitors has highlighted the benefits of damping down this neuroendocrine activation.

HISTORICAL PERSPECTIVES

Before the 1940's, theories on the nature of the circulatory disorder in heart failure abounded but the means of treating the condition were limited. The advent of cardiac catheterisation, methods of measuring regional blood flow and, finally, non-invasive measures of cardiovascular function, have contributed to better understanding of the interplay between the failing heart and the abnormal circulation that it still supports.

While Sharpey-Schafer [530] and McMichael [531] described the relationship between cardiac output and venous pressure in heart failure in the 1940's, Wood [532] recognised the importance of systemic vasoconstriction in the maintenance of blood pressure. These observations were brought together in the 1960's and integrated the concepts of altered preload, afterload and myocardial contractility.[533-535]

As understanding of the pathophysiology of heart failure grew, so did the therapeutic armamentarium. Although the efficacy of digoxin for patients in sinus rhythm has remained controversial,[536,537] no other inotropic agent has yet been more effective or safe.[538]

Mercurial diuretics, introduced in the 1920's, thiazides in the 1950's and loop diuretics in the 1960's all made substantial contributions to the alleviation of symptoms although they may indirectly have had deleterious

haemodynamics and neuroendocrine effects.

The concept of reducing vascular tone in heart failure is remarkably old. Osler (1892) used nitroglycerine[539] and Savill (1936) suggested sympathectomy as a treatment for intractable heart failure[540]. These ideas gained substance in the 1950's, with the use of ganglion- blocking agents[541,542] and nitrates.[543] Since then, nitrates have achieved a lasting place in the management of pulmonary oedema. The use of phentolamine in the 1970's ushered in the "modern" era of vasodilator therapy.[544] However, until the appearance of angiotensin-converting enzyme inhibitors in the 1980's, vasodilators had achieved no firm role in the management of chronic heart failure. In contrast to preceding agents, ACE inhibitors suppress the neuroendocrine consequences of heart failure, but, like them, tend to cause a further fall in arterial pressure.

"DIRECT"-ACTING VASODILATORS

Arteriolar Vasodilators

Daly has shown that in contrast to ACE inhibitors, the combination of nitrates and hydralazine leads to an increase in transmyocardial noradrenaline release which contributes to a rise in arterial noradrenaline, adrenaline and renin.[553] The increase in renin may also be prostaglandin-mediated in part,[554] but is generally not paralleled by an increase in aldosterone, which may reflect effects on hepatic clearance or adrenal release.

Calcium antagonists cause a natriuresis and diuresis when used in very low doses in hypertensive patients, but this effect may be reversed by higher (hypotensive) doses. Whether the same is true in heart failure is unknown. Carefully controlled studies of sodium and water balance after hydralazine are lacking but what evidence there is suggests that fluid retention may occur,[555] whereas minoxidil causes such gross fluid retention that it may be difficult to control with diuretics.[556]

Thus, activation of vasoconstrictor mechanisms, plus salt and water retention, may attenuate the haemodynamic benefits of many arterial vasodilators, and explain the apparent development of tolerance. Despite this, the combination of isosorbide dinitrate with hydralazine appears to favourably affect the prognosis in heart failure.[557] Newer arterial vasodilators such as flosequinan may not activate neuroendocrine systems and initial reports on therapeutic efficacy are encouraging.[559]

Organic and Inorganic Nitrates

These compounds reduce both arteriolar resistance and venous tone. The reduction in preload may limit the increase in cardiac output or even cause it to fall. Tolerance to nitrates is common and appears largely mediated through endothelium-dependent mechanisms. However, activation of the renin-angiotensin system[559] and plasma

volume expansion[560] may also contribute to nitrate tolerance in heart failure. At present, it is uncertain whether intermittent dosing or concomitant administration of N-acetylcysteine can prevent tolerance to nitrates.

Although stimulation of the renin-angiotensin and sympathetic nervous system by sodium nitroprusside is attenuated in heart failure, a rebound increase in vascular resistance may occur after sudden cessation.[561] This may be prevented by phentolamine[562] and is probably mediated through neuroendocrine activation. A reduction in atrial pressure and consequently in plasma atrial natriuretic peptide could also lead to a rise in plasma renin.

There is no convincing evidence that nitrates are effective in reducing symptoms or increasing exercise performance in chronic heart failure, though they are highly effective in acute heart failure by reducing atrial pressure. Studies that purport to show benefit in chronic heart failure are hampered by small numbers, poor study design and variations in diuretic dose.[563,564]

Inodilators

This is a recently-coined phrase for phosphodiesterase inhibitors and dopamine analogues which, although originally thought to act mainly as inotropes, exert many of their effects through vasodilatation.[565] These drugs all tend to reduce vascular resistance and atrial pressure

while increasing cardiac output. Limb blood flow is most strikingly increased, with little efect on renal or hepatomesenteric blood flow.

Phosphodiesterase inhibitors have shown conflicting effects on plasma noradrenaline and arginine vasopressin, though plasma renin increases and atrial natriuretic peptide falls.[566,567] The significance of these findings is as yet unclear.

Clinical studies have generally not shown much benefit during long-term treatment with amrinone or milrinone and survival may even be impaired.[568] Recent studies with enoximone are more promising.[569]

VASODILATORS ACTING THROUGH INHIBITION OR ACTIVATION OF NEUROENDOCRINE SYSTEMS

Alpha-adrenergic Receptor Antagonists

Phentolamine, the first drug of this class to be used in heart failure, inhibits both post-($alpha_1$) and pre- ($alpha_2$) synaptic alpha-receptors. Tachycardia and postural hypotension were common and led to the development of selective alpha-1-receptor antagonists such as prazosin, trimazosin and doxazosin.

Alpha-1-receptor Antagonists

These agents reduce both arterial and venous tone. Limb blood flow is increased, particularly during sub-maximal exercise[570] when sympathetic tone usually limits exercise-induced vasodilatation. However, oxygen extraction does not appear to change.[571] Tolerance is common. Increased sympathetic activity during exercise may be beneficial, at least in mild heart failure, by directing the limited cardiac output to the metabolically most active muscles.[572]

Prazosin is not very selective (about 10:1) and inhibition of the $alpha_2$-receptor may intensify sympathetic and renin-angiotensin system activity.[573,574] This activation, combined with a reduction in atrial natriuretic peptide and renal perfusion pressure may excacerbate sodium retention, reversing the beneficial direct effects of prazosin-induced vasodilatation. Unfortunately, trimazosin, which is more selective, does not appear more effective or less likely to give rise to tolerance. Spironolactone[575] and captopril[576] have both been used to try and prevent fluid accumulation with prazosin, without success.

Clinical experience with these agents again suggests no benefit from vasodilator therapy,[577,578] while some studies demonstrate an adverse outcome.[574,576]

Alpha-2-Receptor Antagonists

Clonidine, a centrally-acting alpha$_2$-receptor agonist, may reduce sympathetic activity. No clinical benefit has been noted.[579] Methyldopa has also been used to reduce central sympathetic activation in heart failure but without objective evidence of benefit.[580]

Drugs acting on Beta-adrenergic Receptors

Beta-1 Receptors

Pure agonists are vasoconstrictive, arrhythmogenic, activate the renin-angiotensin-aldosterone system and, in excess, may cause myocardial necrosis. Antagonists reduce myocardial oxygen consumption and arrhythmias but their negative inotropic qualities sometimes exacerbate failure. Partial agonists such as xamoterol are promising but, as their effects are more on the myocardium than on the periphery, will not be discussed further.

Beta-2-Receptors

Beta-2 agonists have proved disappointing in clinical use. Dopexamine may activate both the sympathetic and renin-angiotensin systems,[581] while rapid tolerance has been demonstrated in some studies.[582] This could be due to neuroendocrine excitation but receptor down- regulation or uncoupling seems just as likely.[583]

Dopamine Analogues

Fenoldopam (a DA_1 agonist) also produces vasodilatation but may activate both the sympathetic and renin- angiotensin systems.[584] Dopamine (DA_2) receptor stimulation by orally active analogues such as bromocriptine may cause a decline in sympathetic nervous activity with consequent vasodilatation.[585] Levodopa and ibopamine may have additional direct inotropic effects.[586,587] However, withdrawal of sympathetic support from the failing heart may counterbalance the benefit of peripheral sympathetic inhibition. Proof that dopamine and its analogues are effective in the management of chronic heart failure is still awaited.

Anti-diuretic Hormone

Arginine $vasopressin_1$-receptor antagonists have little haemodynamic effect in heart failure unless arginine vasopressin is markedly elevated, when a marked reduction in atrial and arterial pressures and an increase in cardiac output may be observed.[588]

Atrial Natriuretic Peptide

Infusion of pharmacological doses of atrial natriuretic peptide in heart failure results in peripheral vasodilatation, an increase in cardiac output and a reduction in atrial pressures. Compared to normal subjects, such patients have a diminished (though not absent)

diuresis and natiuresis, with little change in glomerular filtration rate.[589] Although aldosterone is suppressed and plasma noradrenaline tends to fall, plasma levels of arginine vasopressin are generally unaffected.[590] Plasma levels of renin are also unchanged, suggesting that the stimulus to renin secretion caused by the vasodilatation is balanced by a direct inhibition of renin secretion. Atriopeptidase inhibitors are an alternative method of increasing atrial natriuretic peptide and have been shown to have natriuretic effects in heart failure.[591]

Prostaglandins

Prostacyclin is a powerful vasodilator but has little effect on sympathetic or renin-angiotensin system activity.[592] Infusion of prostaglandin E has similar effects but may also cause renin release.[593]

Bradykinin

Bradykinin degradation is inhibited by captopril and could be responsible for the venodilating effect of captopril. Studies on aprotinin, which inhibits the formation of bradykinin, have failed to demonstrate any attenuation of captopril's effects in heart failure.[594]

Serotonin

Preliminary studies on ketanserin, which selectively blocks 5-HT2 receptors, indicate that it may cause vasodilatation and an increase in cardiac output.[595] Plasma catecholamines

increase, perhaps due to inhibition of neuronal re-uptake.

Renin-Angiotensin-Aldosterone System

Inhibition of the enzyme renin may prove to be the most specific way of preventing angiotensin II formation. Human studies in heart failure are awaited.

Saralasin, a competitive inhibitor of angiotensin II at its receptor, has partial agonist activity, but again experience of its use in heart failure is limited.

CONCLUSION

Although direct acting vasodilators might be expected to improve symptoms and exercise performance in heart failure, they have proved disappointing. Most vasodilators appear to increase blood flow to skeletal muscle but there is no evidence that this leads to increased oxygen utilisation during exercise. There is compelling evidence that administration of vasodilators to patients with chronic heart failure will generally lead to further neuroendocrine activation which may limit their therapeutic efficacy. Angiotensin- converting enzyme inhibitors may circumvent this problem by prevention of angiotensin II formation which in turn will lead to reduced sympathetic activity and aldosterone production.

PART TWO: METHODS AND RESULTS

CHAPTER 7: METHODS

THE ASSESSMENT OF SYMPTOMS

Symptoms were assessed according to the New York Heart Association classification, as outlined in Table 7.1. This is a fairly crude estimate of the severity of heart failure, yet appears meaningful, at least in studies on prognosis in heart failure. New York Heart Association class was also used as a guide to alteration in symptoms after therapeutic intervention but as it was felt that such a division would fail to demonstrate subtle changes, symptoms were also assessed by direct questioning and by visual analogue scores.

Direct Questioning

In some studies, the assessment of changes in symptoms was also made by direct questioning while both doctor and patient were kept "double-blind". In this way, observer and inappropriate patient bias was eliminated. Patients were asked at the end of each part of the study to say whether or not they felt improved. At the end of the trial the patients were then asked to state which period of "therapy" had benefited them most.

This form of symptom assessment is probably the most sensitive index of change but is difficult to quantify.

TABLE 7.1

Criteria for New York Heart Association Functional Classification

I	Patients without limitation of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
II	Patients with slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
III	Patients with moderate limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or anginal pain.
IV	Patients with inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even when the patient is at rest.

Visual Analogue Scores

Visual analogue scores were applied "double-blind", the patient being asked to mark a point on a 10 cm ungraduated line (see examples) corresponding to their symptoms. At the end of each study period the patient was asked to score himself/herself again, but without referring back to the previous scores. The possibility of systematic errors of such a method of assessing symptoms has been suggested. In order to investigate this possibility we studied 20 patients during the open run-in phase of the study on enalapril. Visual analogue scores were applied before and four weeks later, at the end of this run-in period. The results are outlined in Table 7.2. No significant change in mean scores was noted, although there was considerable individual variation. Further evidence for a lack of any systematic drift of scores came from a study on amiodarone in heart failure where a similar scoring system was used.[596] During this double-blind placebo- controlled study of a drug which did not alter symptoms of breathlessness, fatigue or ankle swelling by direct questioning, no change in mean visual analogue scores was noted over a 6-month period.

THE MEASUREMENT OF BLOOD PRESSURE AND HEART RATE

Blood pressure was measured with a Hawksley random zero sphygmomanometer unless measured directly, intra-arterially (vide infra). Pressure readings were taken using a standard forearm cuff with phase I Korotkoff sounds taken

TABLE 7.2

VISUAL ANALOGUE SCORES
n=20

	Run-in period	
	Pre-	**Post-**
Breathlessness (mm)		
mean	58	55
median	64	61
range	16-98	15-92
Tiredness (mm)		
mean	49	51
median	61	58
range	2-100	0-100

as systolic and phase V as diastolic. Mean arterial pressures for this method were calculated as the diastolic pressure plus one-third of the pulse pressure. Heart rate was derived from the apex beat for patients in atrial fibrillation and from the radial pulse in those in sinus rhythm. During exercise testing and tests of autonomic function, heart rate was derived from the electrocardiogram.

THE 12-LEAD ELECTROCARDIOGRAM

The 12-lead electrocardiogram was recorded in the standard manner. QT intervals were measured from the same lead on each occasion; the lead in which the QT interval could most clearly be defined being chosen. The QT was defined by extrapolating the maximal downslope of the T wave to the isoelectric line and measuring the distance to the preceding Q wave.[597] Difficulties arose in the interpretation of the QT interval as many subjects had intra-ventricular conduction defects. The JT interval was therefore also recorded by subtracting the QRS width from the QT interval. QT and JT intervals were also corrected using Bazett's formula.

EXERCISE TESTING IN PATIENTS WITH HEART FAILURE

Exercise using a motorised treadmill was used in preference to a bicycle ergometer as this was thought more closely to simulate the ordinary activity of our patients.

Heart rate was monitored by a 12-lead electrocardiogram, with ST segment monitoring to detect evidence of serious ischaemia or arrhythmias. Blood pressure was monitored with a sphygmomanometer. (vide supra).

Patients were all familiarised with walking on a treadmill on at least one occasion before entering a study. Patients were taught to use a surrounding bar for balance, and taught not to perform isometric exercise (the "wheel-barrow effect") which might have altered oxygen consumption, blood pressure, and exercise performance.

The effects of test familiarisation and the effects of placebo on treadmill exercise performance were assessed separately in 20 patients undergoing exercise (see appended abstract A). In short, exercise time may double from the time of initial exercise to the end of a trial of placebo. Approximately half of the improvement appears to be due to the learning process and half to be due to the introduction of placebo.

Abstract

In patients with chronic heart failure undergoing exercise testing for the assessment of new therapies the relative contributions of familiarisation with the procedure and the so-called placebo effect are uncertain.
Accordingly we assessed the exercise responses in 20 patients with heart failure, mean age 57+9years. The aetiology was ischaemic heart disease in 11, cardiomyopathy in 7 and persisting heart failure after succesful valvar surgery in two. Patients were exercised twice before and once after an open run-in period, prior to randomisation to placebo or a cardioactive drug. The placebo response was then estimated only in those 20 patients randomised to placebo first. This ensured that both the doctor and patient were kept double-blind to prevent a bias towards no response. Four patients who died and 18 patients who received active therapy first were excluded from the final analysis. The active therapies being considered were enalapril and amiodarone. The treatment periods were 2 months and 3 months respectively.
All patients were exercised using a modified Bruce Protocol with heart rate and blood pressure monitoring. Breathlessness or tiredness was the end-point in 76 of the 80 tests performed and sustained ventricular arrhythmias in four. Values are mean ± standard deviation. Analysis of variance was used to test for differences between each test period. When a statistical difference was found student's t-test was used to confirm likely differences.
The initial exercise time was 5.3±3.1 minutes and increased to 7.9±4.6mins ($p<0.01$) at the start of the run-in phase. Exercise increased insignificantly during the run-in phase to 8.4±2.3mins., but after placebo increased further to 10.1±3.9mins.($p<0.01$). Despite the increase in exercise performance, peak exercise heart rate and blood pressure were not statistically significantly different at each time point.
The contribution of the placebo effect seems similar to that of familiarisation with the exercise protocol in this study where placebo was administered double-blind.

As patients with heart failure have a considerably reduced exercise performance compared to healthy controls, protocols were modified accordingly **(Table 7.3)**. Initially, a modified Balke protocol was used in the study on captopril. This was subsequently felt not to be an optimal form of exercise for patients with heart failure and was substituted with a modified Bruce protocol for the study on enalapril. Although both the patients, the exercise protocol, and the benefits of therapy were robust enough to show changes, it became clear that some patients were stopping due to fatigue and others due to breathlessness. This prompted an investigation into differing exercise protocols and their relationship to the symptom terminating exercise in patients with heart failure[598,599] and also their effects on maximal achieved oxygen consumption. In summary, exercise protocols involving very gradual stages were usually terminated by fatigue, whereas protocols which increased speed or inclination rapidly were usually terminated with breathlessness. In the study on angina, 2 "arithmetic" exercise protocols were applied to the patients, one with very gradual increases in workload, the other with much more rapid increments.[598]

In the study of angina and heart failure, cardio-respiratory performance was also assessed by measuring the volume and partial pressures of exhaled gases using a Horizon Mobile Metabolic Cart (Sensormedics). Gas volumes were calculated from the speed of rotation of a finely

TABLE 7.3

	Stage	Time (min)	Speed (mph)	Gradient (%)	Predicted oxygen consumption (ml/min)
MODIFIED BALKE	1	3	2	0	7
	2	3	2.5	4	14
	3	3	3	8	21
	4	3	3	12	28
	5	3	3	16	33
MODIFIED BRUCE	1	3	1.7	0	
	2	3	1.7	5	
	3	3	1.7	10	
	4	3	2.5	12	
	5	3	3.4	14	
	6	3	4.2	16	

tuned turbine, carbon dioxide using infra-red spectroscopy, and oxygen by a polarographic method. In this way oxygen consumption was determined. Maximal oxygen consumption is an index of peak cardiac output during exercise, and appears to be a more reproducible measure of cardiopulmonary performance than exercise time alone.[599,600] Measurement of minute ventilation and carbon dioxide production allows an assessment of the anaerobic threshold.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION

Systolic Time Intervals

Systolic time intervals were calculated from the standard lead II of the electrocardiogram and high quality M-mode echocardiograms of the aortic valve. All recordings were made at a paper speed of 100 mm/sec. Only patients in sinus rhythm were studied thus. The pre-ejection period was measured from the onset of the QRS to the time of opening of the aortic valve. The left ventricular ejection time was measured as the duration of opening of the aortic valve. Electro-mechanical systole was taken as the sum of pre-ejection period (PEP) and the left ventricular ejection time (LVET). Appropriate corrections were made for heart rate for each of these intervals.[601-604]

Changes in pre-ejection period mainly reflect changes in left ventricular preload, assuming that the intrinsic

ventricular function remains constant, a fall in preload leading to a prolongation of the PEP. An increase in afterload may also prolong the PEP. Although left bundle branch block prolongs the PEP, this is of little relevance when within-patients comparisons are made.

The LVET may be prolonged by a fall in afterload or an increase in preload. The reduction in LVET in heart failure is due to a reduction in overall myocardial fibre shortening. The duration of electromechanical systole shortens as the inotropic state of the ventricle increases. The ratio of the pre-ejection period to left ventricular ejection time correlates with angiographically-derived left ventricular ejection fraction.[604]

M-Mode Echocardiography

M-mode echocardiograms were taken with simultaneous two-dimensional echocardiography (IREX) to ensure correct and reproducible orientation. M-mode echocardiograms were analyzed on a dedicated digitising board (KONTRON), with the results of at least 6 cardiac cycles averaged.

The criteria for quantification of the M-mode echocardiogram were those proposed by Sahn[605] and accepted by the American Society of Echocardiography in 1978. These methods have been found to be reproducible by several authors, even when used for repeat measurements over considerable periods of time.[606]

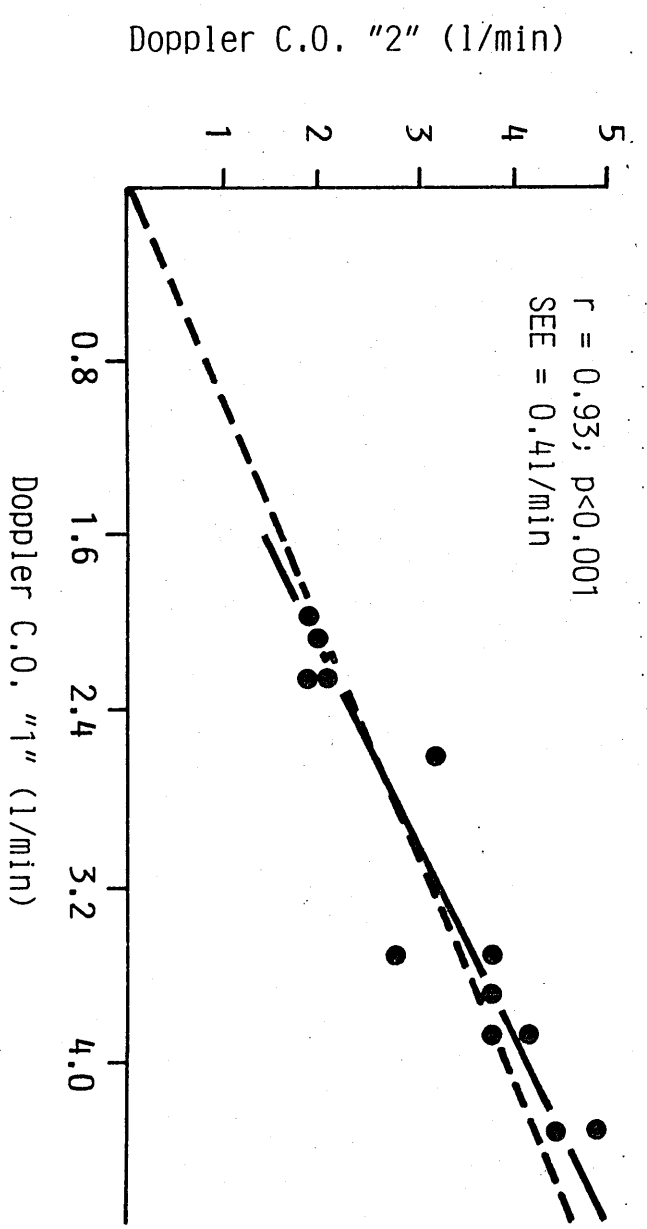
Left ventricular end-diastolic dimensions were timed at the onset of the R-wave and were taken at the level of the tips of the mitral valve leaflets. End-systolic dimension was taken as the smallest perpendicular systolic dimension. Fractional shortening was calculated as left ventricular end-diastolic dimension minus left ventricular end-systolic dimension, divided by the end-diastolic left ventricular dimension.

The use of M-mode echocardiography in patients with heart failure due to ischaemic heart disease has been criticised as regional rather than uniform, global dysfunction is the rule. However, we were making within-patient comparisons, therefore such objections are less important. Incorporation of an infarcted segment in the region measured by M-mode echocardiography could fail to identify improvement in ventricular function at other sites, thus leading to an under-estimate of any improvement with angiotensin-converting enzyme inhibitors.

Doppler Echocardiography

Continuous wave Doppler signals were recorded from the cardiac apex (DOPTEK). Only patients with high quality Doppler signals were chosen for this study. The area under the curve (the velocity-time index) was measured by planimetry and the average of 10 cycles obtained. The outflow tract radius was taken as the aortic valve orifice,

FIGURE 7.1


Doppler C.O. "2" (l/min)
1
2
3
4
5
r = 0.93; p<0.001
SEE = 0.41/min
0.8
1.6
2.4
3.2
4.0
Doppler C.O. "1" (l/min)

according to the method of Ihlen.[607] Stroke volume was calculated as the square of the outflow tract radius x ii x the velocity-time index. Cardiac output was then calculated as heart rate x stroke volume. Doppler-derived cardiac outputs have been compared with cardiac outputs using the thermodilution technique. The largest error in measuring cardiac output appears to be the calculation of the left ventricular outflow tract dimensions. As this probably varies little within a subject over a period of months, the outflow tract dimension was calculated only once, and used repeatedly for serial comparisons.

The reproducibility of this technique in our hands, given suitable subjects, is illustrated in Figure 7.1. For within-patient comparisons, this technique appears satisfactory.

Monitoring Pulmonary and Systemic Arterial Pressure directly

All pressures were recorded with 23Db Stratham transducers placed at mid-chest height, and a multi- channel pen recorder (Mingograph, Elema Siemens). Patients were studied in the supine position, and at least 6 hours after the last meal and last routine medication. Pulmonary arterial pressures were measured by a size 7 Swan-Ganz flow-directed thermodilution catheter inserted via an antecubital vein into the pulmonary artery. Cardiac output was measured from

3-5 sequential injections of 10 ml of chilled 0.15M saline solution. Output was calculated from a model 9520A Ed wards computer. Arterial pressures were measured via a radial artery cannula and recorded by a Gould P23 ID transducer. Mean pressures were obtained by electronic integration.

Radionuclide Ventriculography

Patients were injected with 1-3 mg of stannous pyrophosphate, 15 minutes prior to injection with 550 MBq of ^{99m}-Technetium to label the patients' own red blood cells.

Rest and exercise ejection fractions were assessed by multiple uptake gated acquisition, triggered from the R-wave of a simultaneous ECG recording, and a multi- crystal gamma camera. Images were acquired in the supine position, with bicycle exercise also supine, starting at a 25 Watt load and increasing by 25 Watts every 2 minutes.

Resting images were acquired over 600 cardiac cycles and exercise images over 300 cardiac cycles.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Ambulatory electrocardiographs were recorded for 48 hours using a Medilog I system (Oxford). Electrodes were placed in the modified V1 or V5 positions and checked for satisfactory impedance values before connection to the recorder. Tapes were analyzed using a semi- automated

playback system at 60 times normal speed, with expert visual supervision and without knowledge of the patients' cardiac or treatment status. The frequency of ventricular extra-systoles and couplets were counted, while more complex arrhythmias were printed for later consideration. Ventricular salvoes were defined as 3 or more consecutive beats at any rate and ventricular tachycardia as 3 or more consecutive beats at more than 120 beats per minute.

THE MEASUREMENT OF RENAL FUNCTION

Several measures of renal function will be reported in this thesis. At its most simple, serum urea and creatinine are a useful reflection of renal function; monitoring these proved a useful guide to the glomerular filtration rate in this study. Serum urea and creatinine will reflect the cumulative effects of several days of renal function, and thereby may be markers of changes in renal function to a variety of stimuli, eg, exercise, etc, which will not be observed under the more controlled conditions outlined below.

However, both compounds are incompletely filtered at the glomerulus and both show variable reabsorption and excretion in the renal tubule. That angiotensin converting enzyme inhibitors can alter tubular function as well as glomerular filtration seems certain, therefore more detailed and precise methods of measuring renal function

are warranted. However, measurement of glomerular filtration rate by the other methods in this study reflect renal status over relatively short periods of time.

Clearance of substances by the kidney with measurements in blood and urine constitutes the second method of measurement. We have measured renal clearance of digoxin as well as sodium, potassium, magnesium, phosphate, urea and creatinine. For the determination of the clearance of urea and creatinine, 24 hour urine collections with paired sera, from the beginning to the end of the collection period, were used. In those studies using digoxin and phosphate clearance, 6 hour urine collections were made. This shorter collection period allowed us to study patients with heart failure before and after they received their required daily treatment with diuretics. This is important as diuretics such as frusemide necessarily affect renal tubular function and are therefore likely to alter drugs which undergo tubular excretion or reabsorption. Clearance was calculated by calculating the mean serum level over the six hours from timed samples at the start of the urine collection, at 3 hours and at 6 hours. Digoxin was always given at least 6 hours before starting urine collections to ensure that the peak drug concentration occurred before sampling and that a relatively simple decay curve was being observed.

Thirdly, single radio-isotope injection techniques were used to measure glomerular filtration rate (40 MBq ^{99m}-

Technetium-DTPA or ^{51}Cr-EDTA) and effective renal plasma flow (1 MBq of chromatographically pure ^{131}I- hippuran or ^{125}I-hippuran).[608-610] The volumes used were 4 ml and were accurately measured. Patients were kept on strict bed rest for the period of study and were always given exactly the same treatment apart from the drug under scrutiny (ie, captopril, enalapril or frusemide), and were always studied at the same time of day and with the same relationship to meals. Six ml plasma samples were taken from the opposite arm into lithium-heparin tubes at baseline (for a background count) 20 minutes, 45 minutes, 2, 3, 4 and 6 hours after injection. Analysis of over 100 studies revealed that the background, 45 minute and 2 and 4 hour samples carried all the useful information and subsequently analysis was performed using only these samples. Renal blood flow was calculated from the following formula: renal blood flow = effective renal plasma flow x 1- haematocrit. As not all the blood flowing to the kidney passes through a glomerulus (ie blood flow to the renal papillae) and since ^{131}I-hippuran is not 100% extracted in the glomerular filtrate, measurement of renal blood flow may be underestimated. Angiotensin converting enzyme inhibitors may decrease the efficiency of renal hippuran extraction. The measurements of renal blood flow that I have used may have underestimated the increase in renal blood flow during ACE inhibition to a proportionally greater extent.

Renal vascular resistance was calculated as: 80 (mean arterial pressure (mm Hg) x (renal blood flow (l/min)).

The filtration fraction was taken as the ratio of the glomerular filtration rate to the effective renal plasma flow, as by convention.

Using data obtained from baseline and placebo phases of the clinical trials we have performed, the standard error of the estimate was 3 ml/minute for the glomerular filtration rate and 32 ml/minute for effective renal plasma flow. The difference in accuracy between the two measures may reflect some inferiority in the techniques for measuring plasma flow. However, physiological control of glomerular filtration is tightly held while renal blood flow is much more variable, which could also account for the observed difference.

Tubular Function

Tubular function was assessed from the fractional excretion of sodium, potassium and phosphate. For these studies, patients were admitted to the ward and commenced on diet with 100 mmol sodium, 40 mmol potassium and 2,500 ml fluid, 48 hours prior to the study. The amount of electrolyte filtered at the glomerulus was calculated by multiplying the creatinine clearance by the mean plasma concentration of the electrolyte obtained from 3 samples over the 6-hour study period. Urine volumes were measured over 6 hours and

the urinary concentration of electrolytes calculated. The fractional excretion of electrolyte was expressed as that percentage of the electrolyte filtered at the glomerulus that was actually found in the urine. Whereas sodium is absorbed by a variety of mechanisms throughout the length of the renal tubule, phosphate is largely reabsorbed in the proximal tubule.[611] Potassium may be reabsorbed at several sites along the renal tubule but may be exchanged for sodium in the distal tubule under the influence of aldosterone. (See Chapter 2).

PLASMA VOLUMES

Plasma volumes were estimated by measuring plasma radioactivity before and 10 minutes after the injection of ^{125}I-human serum albumin. Blood volume was calculated using the haematocrit. It was assumed that the red cell mass was constant over periods of less than 3 days, allowing short term serial follow up of plasma volume.

THE ANALYSIS OF WHOLE BODY COMPOSITION

The Measurement of Total Body Potassium

Total body potassium was derived from endogenous ^{40}K using a sodium iodide detector with both the patient and detector shielded by 10 cm of lead. The patient passed the detector at a uniform speed on a motorised couch, first supine, then prone in the reverse direction. The estimated coefficient

of variation is ±3.9% for a subject with 3,600 mmol of potassium.[612] This method has been validated using phantoms containing a known quantity of potassium (^{40}K) in solution by Lye et al, who found a similar level of accuracy.[613]

Total Body in-vivo Neutron Activation Analysis

Total body sodium, chlorine, calcium, phosphorus, nitrogen and oxygen were measured simultaneously by total body in-vivo neutron activation analysis using two sealed tube 14 MeV generators.[614-627] Subjects lay on a motorised couch which passed between the neutron tubes at a constant speed of 52 mm/second and received a simultaneous bilateral scanning irradiation. The radiation dose received was one REM (10 MsV) at the body surface.

Induced radioactivity was then measured in a high sensitivity shadow shielded whole body counter using 2 large sodium iodide detectors by repeated counting scans for up to 30 minutes after irradiation. The following reactions were examined and from calculation of the induced radioactivity the total amount of each element shown was calculated.

Table 7.4

Element	Reaction	t/2 (minutes)	%S.D.*
Sodium	^{23}Na-^{24}Na	901.80	2.9
Chlorine	^{37}Cl-^{38}Cl	37.18	4.0
Calcium	^{48}Ca-^{49}Ca	8.72	3.5
Phosphorus	^{31}P -^{28}Al	2.24	2.1
Nitrogen	^{14}N -^{13}N	9.97	2.2
Oxygen	^{16}N -^{14}N	0.12	2.9

*Derived from variance in repeated measurements on phantoms of known consistency.[614,615]

This technique has been extensively validated against "phantoms" of varying size with known chemical composition and shown to be highly accurate and reproducible. Measurements have also been made in animals which were subsequently cremated and then analyzed for body composition. These have also substantiated the validity of the technique. Limited data are available on reproducibility in man due to the relatively high radiation

exposure required for repeat studies. Patients with heart failure have a poor prognosis, therefore repeat studies were ethically permissible.

Total body sodium is made of 2 main components. A "rapidly exchangeable" component is present largely in the extracellular space though intracellular sodium may increase in heart failure. A second, "slowly exchangeable" component, comprising about 25% of all sodium, is present largely in bone.[619]

Chloride is mostly present in the extracellular space and is almost entirely exchangeable.[622] Total body chlorine correlates well with bromide space and extracellular fluid volume may be calculated by dividing total body chlorine by serum chloride concentration with a 10% reduction to allow for intracellular chloride.

Calcium and phosphorus are largely present in bone and show little change except over long periods of time. However, they form a useful standard for studies performed weeks apart.

Nitrogen is an index of protein mass: muscle, collagen and the viscera being the major sites of this element. Therefore, nitrogen is a useful index of lean body mass.

Most of the element oxygen is present as water. This measurement is an index of total body water.

Values are expressed in millimole for sodium, potassium and chlorine, in grams for calcium, phosphorus and nitrogen, and kilograms for oxygen. Results for whole body elements were also compared with and expressed as a percentage of predicted values for healthy subjects matched for height, weight, age and sex. The normal values for total body potassium were predicted from those obtained by Boddy et al.[612] Potassium was also expressed as mmol/g of nitrogen, as suggested by Burkinshaw and Morgan.[623]

Normal values for sodium and calcium were derived from measurements by Ellis et al.[620] Equations for the prediction of chlorine were based on measurements of extracellular fluid space using radioactive bromine. "Dry" weight was estimated in the heart failure group by correcting their extracellular fluid weight to that of controls. Predicted values for total body nitrogen were derived from the formula N (g) = 322 x height3 + 81.[624]

Phosphorus and oxygen have not been measured in normal subjects. No correction is possible for oxygen. However, phosphorus and calcium are closely related so this ratio may be used to "normalise" phosphorus measurements.

TESTING THE AUTONOMIC NERVOUS SYSTEM

A) Parasympathetic Function

1) The Valsalva Ratio

In normal subjects, during the strain period of the Valsalva manoeuvre, the blood pressure drops and the heart rate rises. After the release, the blood pressure rises, overshooting its resting value as the heart slows. The heart rate changes can be abolished by atropine but are unaffected by popranolol, suggesting that the responses are mediated via the parasympathetic nervous system.[628] In patients with autonomic damage, heart rate changes little.[629]

For the present experiments, the patient was asked to blow into a modified mercury sphygmomanometer for 15 seconds while maintaining a pressure of 40 mm Hg. The heart rate response was measured by continuously monitoring the electrocardiogram. The result was expressed as a ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the manoeuvre. A mean from three tests was used.

2) The R-R Interval during deep breathing

Heart rate varies continually in normal subjects. This "high frequency" variation is abolished by atropine but uninfluenced by popranolol.[630] Patients were requested to breathe in and out deeply at 5 second intervals while continuously recording the electrocardiogram for one

minute.[631] The mean change in heart rate over 6 cycles, from the largest R-R interval (expiration) to the shortest (inspiration) was calculated.

3) The immediate Heart Rate Response to Standing

On standing upright, an immediate rapid increase in heart rate occurs which is maximal around the 15th beat and then a relative overshoot bradycardia occurs, maximal about 30th beat.[632] This is also mediated by the vagus nerve.[633] The longest R-R interval around the 30th beat was expressed as a ratio of the shortest R-R interval around the 15th beat.

B) <u>Sympathetic Function</u>

1) Posture

On standing, pooling of blood in the legs causes a fall in blood pressure which is normally rapidly corrected by peripheral vasoconstriction. This is dependent upon many mechanisms and appears to involve important sympathetic reflexes. The blood pressure and heart rate were recorded after 15 minutes rest in the supine position and after 2 minutes standing. In addition, changes in plasma noradrenaline were measured.

2) Exercise Testing refs 628,630

Exercise is associated with an increase in heart rate, cardiac output and arterial blood pressure, associated with a reduction in systemic vascular resistance. The

tachycardia associated with exercise can be markedly reduced with a beta-blocker. Circulating catecholamines rise during exercise. The blood pressure and heart rate response during dynamic exercise therefore appeared at least partially mediated through the sympathetic nervous system, though the initial increase in heart rate during exercise is mediated through parasympathetic withdrawal.

Exercise capacity was determined using a modified Bruce protocol with 3 minute stages. Blood pressure and heart rate were compared at the last fully completed stage of the shortest exercise test for intra-subject comparisons at different time points.

BIOCHEMISTRY

The Timing and Method of Sampling

All samples were withdrawn from forearm veins, apart from one study when samples for catecholamines, renin and angiotensin II were withdrawn from an in-dwelling arterial cannula.

For most studies a rigid standardisation of the timing and circumstances of sampling was adopted.

Unless otherwise stated, venous blood was drawn between 8 am and 9 am from an in-dwelling cannula, the patient having

fasted, apart from water, and remained supine overnight. All drugs, including investigational drugs, were withheld until samples had been taken.

Sampling times and circumstances varied in individual studies but in each case rigid criteria were set and adhered to so that comparisons could be made both between and within individual patients or volunteers.

Electrolytes, Urea and Creatinine

These were measured on a multi-channel analyzer, using an ion-selective electrode.

Digoxin

Serum digoxin was measured using a fluorescent polarisation immunoassay. Urine digoxin was measured by diluting urine with "blank" (non-digoxin containing) serum. This assay is specific for digoxin and its metabolites digoxigenin and mono-and bis-digitoxside.[634]

Urinary digoxin clearance was calculated from the urinary digoxin concentration multiplied by the volume passed over 6 hours. The mean serum digoxin over the sampling period was calculated from the mean of three plasma samples. All studies were commenced 6 hours after the last dose of digoxin. The fractional excretion of digoxin was calculated from the amount excreted in the urine divided by the amount filtered at the glomerulus (mean serum digoxin

concentration multiplied by the creatinine clearance).

SPECIAL BIOCHEMISTRY

Plasma Active Renin Concentration refs: 635-637

(Normal range for the laboratory 10-50 U/ml)

The assay was based on an antibody-trapping method. Blood samples (5 ml) were collected into chilled containers containing EDTA as anticoagulant. Centrifugation and separation of plasma was completed within 1 hour. Plasma was stored at -20 °C until assayed.

Tubes for incubation contained 35 Ul of plasma, ox renin substrate (40 Ul), buffer "3" (10 Ul), and angiotensin I antiserum at appropriate dilution (5 Ul). The last 3 constituents were pre-mixed in the ratio 8:2:1 and 55 Ul of the mixture was added to each tube. Tubes were incubated at 37°C for 30 minutes. This period of incubation usually generated sufficient angiotensin I to read against the sensitive portion of the standard curve. Unusually low and high renin samples were incubated for longer, or in dilution. The renin reaction was terminated by addition of buffer "1" (1.4 ml at 4 ° C), followed by angiotensin I^{125}(50 Ul;20 pg). For radio-immunoassay of angiotensin I, the tubes were then incubated at 4 °C for a further 48 hours. Free and antibody-bound radioactivity were separated using Dextran-coated charcoal (150 Ul), and the pellet was counted in a spectrometer. Plasma renin concentration was derived from the reaction velocity (ng/ml/hour) by

interpolation of a calibration curve, prepared with varying concentrations of the International Standard Renin contained in buffer "2" (35 Ul).

Angiotensin II refs: 638-640

(Normal range for the laboratory 5-35 pmol/l)

Twenty mls of blood were taken directly into tubes containing an inhibitor solution to prevent generation of angiotensin II from angiotensin I and to prevent the degradation of angiotensin II to the octapeptide and smaller peptide fragments. The inhibitor solution contained 0.125 M EDTA and 0.025 M o- phenanthroline in distilled and freshly boiled water, containing 0.2% neomycin sulphate. Angiotensin in the supernatant was absorbed onto Dowex-H^+ in a batch extraction and subsequently eluted with ammonia. The eluate was dried at 37 °C under an air stream: half of the residue was used for the anti-serum incubation.

Antibodies against Asn^1-Val^5-angiotensin II were raised in rabbits using a minor modification of a method described by Goodfriend et al.[640]

Incubation was carried out in 0.5 ml Tris buffer at 4 °C for 2 days. The concentrations of anti-serum and of label (^{125}I-Asn^1-Val^5-angiotensin II) were varied depending upon the assay range. Twenty picograms/ml of label and a 1:16,000 dilution of anti-serum were usually used.

The recovery of angiotensin II from blood was 83% ± 11% (SD). The within assay coefficient of variation was 8.9% and the between assay coefficient of variation 12.3%.

During inhibition of the converting enzyme, angiotensin I levels rise, although the angiotensin II and antiserum used in our analysis has a low cross-reaction (less than 1%) with angiotensin I. With the low levels of angiotensin II and high levels of angiotensin I under these circumstances falsely high values for angiotensin II may be obtained. Accordingly, a correction factor was introduced.[642]

Aldosterone ref: 641

(Normal range for the laboratory 150-500 nmol/l)

Aldosterone was measured by radio-immunoassay. Neutral extracts of 2 ml of plasma, containing 25,000 cpm of ^{3}H-labelled aldosterone (50 Ci/mmol) were chromatographed on a Bouche B5 type chromatography system. The aldosterone region was located by means of isotope scanning equipment and was diluted drop wise with methanol (5 ml). Portions of the eluate were assayed for ^{3}H recovery, and by using this information duplicate samples containing 5,000 cpm of ^{3}H were removed for radio-immunoassay. Ethylene glycol (5% V/V;.1 ml) was added to the samples and standards at this point.

The samples, together with standards ranging from 0 - 200pcg of aldosterone, each containing 5,000 cpm of ^{3}H-

labelled aldosterone, were evaporated to dryness at 30°C in a vacuum oven. The residues were then dissolved in anti-serum solution (0.5 ml;1:500,000 in 0.05 mmol/litre of borate buffer, Ph 7.5, containing 2% (V/V) methanol and 0.5% (W/V) bovine gamma globulin), and incubated at room temperature for one hour, and then at 4°C for at least one hour. Free steroid was absorbed by means of a Dextran-coated charcoal solution. After centrifugation at 4°C, 0.5 ml of the supernatant was assayed for ^{3}H content by accumulating 10,000 counts.

Anti-diuretic Hormone refs: 644,645

(Normal range for the laboratory: 0.3-0.7 pg/ml)

Blood samples for anti-diuretic hormone measurement were stored in iced water until centrifuged at 4°C when the plasma was separated and stored at -20°C. In view of the observations that ADH binds to platelets,[644] care was taken not to remove the plasma immediately above the red cells. Anti-diuretic hormone was extracted from plasma using pre-packed C_{18} reverse phase cartridges (SEP-PAK, Waters Associates, Milford, Massachusetts, USA). Cartridges were initially washed with methanol (5 ml), followed by distilled water (5 ml). Three to five ml of plasma was applied to the cartridge under gentle vacuum, followed by washing with 15% acetic acid (5 ml). Anti-diuretic hormone was eluted from the column by washing with methanol (2 ml). The methanol extracts were dried under a stream of air and the dried extracts dissolved in 50 mmol/litre Tris with a

pH of 7.4 for assay.

A sensitive and specific anti-diuretic hormone anti- serum (72/IV) was used.[645] This anti-serum was raised in New Zealand white rabbits by immunisation with anti- diuretic hormone conjugated to bovine thyroglobulin.[645] Standard ADH (0 - 4 pcg) or unknown extract was incubated with ADH anti-serum at a final dilution of 1:75,000 and ^{125}I- ADH (0.5 pcg, New England Nuclear, Dreich, West Germany) for 48 hours at 5°C. Bound and free anti-diuretic hormone were separated using Dextran- coated charcoal.

The within-assay coefficient of variation was 6.1% and the between assay coefficient of variation was 10.8%.

Catecholamines refs: 647,648

(Normal range (resting) for the laboratory: 0.8-1.2 nmol/l)
Blood samples were taken into chilled tubes, and kept at 4°C, immediately centrifuged, deproteinated by adding 1 molar perchloric acid in a ratio of 1:4 and plasma stored at -20°C for analysis. Samples were measured by the radio-enzymatic method of Da Prada and Zurcher.[647] Briefly, the catecholamines are converted into their 3- methoxy derivatives in the presence of crude catechol-O- methyl transferase and S-adenosyl-L (methyl^{3}H) methionine. The following modifications were included:

1) Ethylene glycol bis-amino ethyl ether tetracetate (3 mmol/litre) was added to the plasma samples.

2) Tris (1 mol/litre), magnesium chloride (75 mmol/litre), benzyloxamine (a dopa-D-carboxylase inhibitor, 0.5 mmol/litre), 20 Ul of catechol-O-methyl-transferase solution and 3.6 UCi of S-adenosyl-L-(methyl-^{3}H) methionine (5-15 Ci/mmol; Amersham, Bucks). The total incubation volume was 150 Ul, and pH 8.43.

3) The 3 methoxy derivatives were extracted into 1 ml of ether, in the presence of tetra-phenylboron and back extracted into 50 Ul of hydrochloric acid (0.1 mmol/l). This was applied directly to thin layer chromatography. Noradrenaline and adrenaline derivatives were extracted into 1 mmol of ammonium hydroxide (0.05 mol/l) and converted into vanillin by the addition of 50 Ulof 4% (W/V) sodium periodate. After 5 minutes, 1 ml of acetic acid (0.1 mmol/l) was added, and the vanillin extracted into toluene containing 0.6% 5-(bi-phenyl-4-yl)-2-(4-butylphenyl) -L-oxa-3,4,diazole. The limit of detection calculated as twice the blank value was 0.1 nmol/l for noradrenaline and adrenaline. The inter-assay coefficient of variation for noradrenaline was 8.6, and adrenaline 11.2%.

As mentioned above, venous sampling was generally employed which does appear to reflect overall sympathetic activity.[648,649] However, some observers suggest that a large contribution to the measured level of catecholamines may derive from the capillary bed which is subserved by the vein used for sampling. In one study, where changes in catecholamine levels were being sought over a short period,

arterial sampling was used by preference to overcome this possible criticism.

Atrial Natriuretic Peptide refs: 651-651

(Normal range for the laboratory: undetectable-80 pg/ml)

Blood was collected in chilled plastic tubes containing EDTA as an anticoagulant and sufficient Trasylol to give a final concentration of 50 kIU/ml. Each sample was transported on ice and centrifuged at 1000g for 10 minutes at 4°C. Atrial natriuretic peptide was extracted from 1-3 ml of plasma on C18 reverse phase columns (Sep-pak, Waters Associates). Sep-paks were pre-activated with 5 ml of methanol and washed with 5 ml of distilled water before application of acidified plasma (0.25 ml 2N hydrochloric acid/ml plasma). The cartridges were then washed three times with 5 ml 0.1% vol/vol trifluoroacetic acid, and the absorbed peptide was eluted with 2 ml 60% acetonitrile/0.1% wt/vol into plastic tubes. The extracts were dried down under compressed air and reconstituted in 0. 5 ml buffer (100 mM sodium phosphate, pH 7.4 Triton X-100, and 50 kMU Trasylol/ml). Antibodies to human atrial natriuretic peptide were raised in New Zealand white rabbits. The antibody used for the radio-immunoassay gave 50% binding of 2 g 125I-human atrial natriuretic peptide (Amersham International) at a dilution of 1/ 33,000. Cross reaction of the antibody with a variety of synthetic atrial natriuretic peptide sequences (5-28 human atrial natriuretic peptide, 7-28 human atrial natriuretic peptide,

atriopeptins I, II and II, and rat atrial natriuretic peptide) was greater than 90%. No significant-cross reactions with cardiodilatin, bradykinin, arginine vasopressin, angiotensins I or II or adrenocorticotrophic hormone were seen. For the assay set up in duplicate, 100 Ul antibody at a dilution of 1/10,000, and 2 pg labelled human atrial natriuretic peptide in 50 Ul buffer were incubated at 4 oC for 24 hours. Free and bound ligands were separated by adding 1 ml charcoal-coated dextran. The mixture was immediately centrifuged for 10 minutes (1000 g at 4 oC) and the free label counted. Non-specific binding of human atrial natriuretic peptide, estimated by adding excess synthetic human atrial natriuretic peptide (5 ng/tube) was consistently 3-4% both in standard solutions and in reconstituted plasma extracts; hence, no correction for binding was required.

Radio-labelled synthetic alpha human atrial natriuretic peptide (20 pg) added to 3 ml plasma before extraction was recovered at a mean rate of 91 $\pm$6%. Recovery rates of cold synthetic human atrial natriuretic peptide added to 3 ml of plasma at concentrations of 100 pg/ml and 500 pg/ml were 86 $\pm$9% and 91 $\pm$8% respectively. Inter-assay and intra-assay coefficients of variation were 7.8% and 7.5% respectively.

CHAPTER 8: THE METABOLIC CONSEQUENCES OF HEART FAILURE AND THE INFLUENCE OF NEUROENDOCRINE ACTIVATION

INTRODUCTION

After many years of debate, there is still controversy about the prevalence, extent, and relevance of potassium depletion in patients treated with diuretics for heart failure.[652-657] While some investigators have documented reduced body potassium levels in such patients, this has been attributed to lack of good con trol data or to muscle wasting as a manifestation of "cardiac cachexia".[652] Some of the difficulties may have arisen due to the absence of a definitive diagnosis of heart failure which the advent of modern diagnostic techniques, in particular echocardiography, has largely resolved. Also, the measurement of total exchangeable potassium requires a prolonged equilibration time after the administration of radioactive tracers which can introduce inaccuracies.[656,658] Measurement of total body potassium using the endogenous 40K isotope avoids this difficulty. Other problems are presented in defining adequate control groups for comparison. Body elemental composition is highly dependent on body mass, adiposity, age, and sex.[659] Control groups have rarely been adequately matched with patients in heart failure, nor have the appropriate corrections usually been made.

Patients with severe heart failure have a poor prognosis, the one year survival for a patient with New York Heart

Association Class III heart failure being approximately 50%.[660,661] Interest in potassium depletion in heart failure has renewed since the obser vation that potassium depletion can be corrected, arrhythmias reduced, and possibly prognosis improved with the use of angiotensin-converting enzyme inhibitors.[662,663]

The technique of in-vivo total body neutron activation analysis performed on the same day also has allowed us to measure total body sodium, chlorine, phosphorus, calcium, and nitrogen. Nitrogen is an index of protein mass,[664] muscle, collagen, and the viscera being the major sites of this element.[665] Measurement of body nitrogen allows a correction for leanness. The element oxygen is mainly present in the body as water and is therefore an index of this constituent.

In-vivo neutron activation analysis requires a fairly large dose of radiation and is not permitted in normal subjects. However, endogenous 40K measurements followed by activation analysis to assess body composition have been employed in untreated patients with essential hypertension,[666] and do not differ from normal values. In addition, we have measured total body potassium in a large series of normal subjects and found no difference from the mean value in untreated essential hypertensives matched for age and sex.[667,668] We have therefore compared patients treated for heart failure with diuretics and digoxin to patients with untreated

essential hypertension and to normal subjects matched for height, weight, age and sex.

PATIENTS

Forty patients referred to the cardiac department for further investigation and treatment of heart failure were compared with 20 subjects without evidence of cardiac or other pathology, and 20 patients with untreated essential hypertension. Heart failure was confirmed by measurement of a raised left ventricular end-diastolic pressure (>16 mm Hg) and poor stroke volume on left ventricular cine-angiography, and a fractional shortening on M mode echocardiography of less than 20% (14±3%;mean ±SEM) with end-diastolic dimension greater than 6 cm (6.4±0.2 cm). The aetiology of cardiac failure was ischaemic heart disease in 20, idiopathic (dilated) cardiomyopathy in 17, and severe residual left ventricular function after successful valve replacement in 3 (2 aortic, one mitral and aortic). Nine were in early NYHA Class IV heart failure but did not suffer undue orthopnoea, 18 in NYHA Class III and 13 in NYHA Class II. All patients had received at least 80 mg/day frusemide (mean 147±13 mg/day) for more than 3 months (mean duration 11±5 months). In addition to frusemide, 5 were taking bendrofluazide 5-10 mg/day. Twelve subjects were taking potassium chloride in a mean daily dose of 2.1±0.1g, but none was receiving potassium-sparing diuretics.

All the hypertensive group were asymptomatic and also

without clinical, biochemical or radiological features of heart failure, aortic coarctation, Cushing's syndrome, primary hyperaldosteronism, renal disease or phaeochromocytoma. Any previous treatment had been withdrawn at least 4 weeks before measurements were made.

METHODS

In each subject nude weight and height were measured. Blood pressure was recorded with the patient supine.

Total body potassium, sodium, chlorine, oxygen, nitrogen, calcium and phosphorus were measured in the hypertensive subjects. Elements other than potassium alone were not measured in normal subjects due to the ethical issues noted above. Blood was drawn from patients who were fasting and supine overnight at 9 am, and again at 4 pm, after 30 minutes supine after usual therapy; sodium, potassium, chloride, urea, creatinine and phosphate were measured and results expressed as the mean of the two values. In addition, plasma concentrations of active renin, angiotensin II and aldosterone were determined from the 9 am sample, using methods previously determined.

STATISTICAL METHODS

Between-group analysis was made using students t-test or the Wilcoxon rank sum test for non-parametrically distributed variables. Results of body elemental composition for patients with heart failure and

hypertension were expressed as the ratio of calculated to predicted normal, 100% representing no difference between calculated and predicted values. Values are expressed as mean ±standard error of the mean for normally distributed data, or mean, median and range where the data is not normally distributed. A single parameter t-test was used to test for systematic deviation from predicted normal values. Significance was taken at the 5% level. Correlations were performed using the method of least squares for variables with bivariate normal distribution and Spearman's rank correlation for non-parametrically distributed data.

RESULTS

Anthropomorphic Measurements (Table 8.1)

The normal subjects and patients with hypertension and heart failure were similar in respect to height, weight, age and sex. Sub-groups of heart failure patients with normal and elevated renin were similar, and each did not differ from the normal or hypertensive group. The similarity in weight persisted even when the heart failure group's weight was corrected for their higher extracellular fluid volume **(Table 8.2)**.

Blood Pressure

Though the blood pressure in the hypertensive group was not greatly elevated (170±3/105±3 mm Hg), mean blood pressure was significantly greater than in those with heart failure

Table 8.1 *Comparison of total body potassium in normal subjects and in patients with hypertension and heart failure*

	Normal (16M/20F) Mean			*Hypertension (15M/20F) SEM*			*Heart failure (32M/40F) Range*		
	Normal	*Hypertension*	*Heart failure*	*Normal*	*Hypertension*	*Heart failure*	*Normal*	*Hypertension*	*Heart failure*
Age (years)	52	53	56	3	3	1	31–72	30–71	28–64
Height (cm)	170	168	167	2	2	1	154–184	151–186	146–180
Weight (kg)	69	69	68	2	3	2	47–92	44–109	45–88
Total body potassium (mmol)	3208	3250	2831*†	131	171	93	2315–4274	2043–4951	1518–4031
Total body nitrogen (g)	1642	1640	1688	51	59	49	1239–2093	1128–2109	1090–2285
Total body potassium: nitrogen ratio (mmol:g)	1·95	1·97	1·68‡§	0·04	0·05	0·03	1·67–2·35	1·54–2·35	1·34–2·09

*p 0·02 *vs* normal; †p 0·05 *vs* hypertension; ‡p 0·0001 *vs* normal; §p 0·0001 *vs* hypertension.

Table 8.2 *Comparison of measurements in patients with hypertension and heart failure*

	Hypertension	*Heart failure*	*p*
Weight (kg)	69 (3)	68 (2) 67 (3) (corrected for ECF)	NS
Mean blood pressure (mm Hg)	126 (3)	94 (3)	< 0·001
Serum sodium (mmol/l)	141 (1)	138 (1)	< 0·05
Serum potassium (mmol/l)	4·2 (0·1)	3·6 (0·1)	< 0·005
Serum chloride (mmol/l)	102 (1)	98 (1)	< 0·05
Serum bicarbonate (mmol/l)	27·5 (0·5)	29·3 (0·4)	< 0·02
Serum urea (mmol/l)	4·7 (0·3)	6·6 (0·4)	< 0·005
Serum creatinine (μmol/l)	90 (3)	102 (4)	< 0·05
Urea:creatinine ratio	51·7 (0·2)	64·4 (2·7)	< 0·005
PARC (μU/ml)	24 (5)	215 (46)	< 0·005
Plasma angiotensin II (pmol/l)	23 (1)	64 (9)	< 0·005
Plasma aldosterone (pmol/l)	331 (32)	729 (117)	< 0·005
Total body potassium (mmol)	3250 (171)	2831 (93)	< 0·05
Total body potassium (%)	103 (89–110)	95 (67–117)*	< 0·01
Total body nitrogen (g)	1640 (59)	1688 (49)	NS
Total body nitrogen (%)	100 (92–117)	106 (86–133)†	NS
Total body potassium:nitrogen (mmol:g)	1·97 (0·05)	1·68 (0·03)	< 0·0001
Total body potassium:nitrogen (%)	103 (97–108)	91 (74–106)‡	< 0·001
Total body sodium (mmol)	3160 (113)	3473 (88)	< 0·05
Total body sodium (%)	98 (89–104)	108 (92–129)	< 0·001
Total body chlorine (mmol)	1697 (70)	1748 (55)	NS
Total body chlorine (%)	96 (86–110)	104 (87–142)	NS
Extracellular fluid volume (ml)	16·7 (0·6)	17·9 (0·5)	NS
Extracellular fluid volume (ml/kg)	242 (9)	266 (6)	< 0·02
Total body calcium (g)	960 (37)	998 (23)	NS
Total body calcium (%)	98 (89–112)	106 (83–121)†	NS
Total body phosphorus (g)	534 (20)	542 (13)	NS
Total body phosphorus:calcium (g:g)	0·56 (0·0·)	0·54 (0·01)	< 0·02

ECF, extracellular fluid volume; %, percentage of normal predicted; PARC, plasma active renin concentration.
*$p < 0·05$, †$p < 0·001$, ‡$p < 0·001$ compared with predicted normal (see text).
Values are mean (SEM) for absolute values and mean and range for percentage values.

Table 8.3 *Total body oxygen in patients with hypertension and patients with heart failure*

	Hypertension	*Heart failure*	*p*
No	7	32	
Total body oxygen (kg)	42·9 (3·0)	36·0 (2·3)	< 0·05
Total body oxygen (%)	104 (89–112)	93 (76–109)	< 0·01
Total body oxygen (kg/kg body weight)	0·59 (0·05)	0·54 (0·07)	< 0·01
TBK/TBO (mmol/kg)	80 (5)	79 (9)	NS
TBNa/TBO (mmol/kg)	79 (8)	95 (9)	< 0·001

TBO, total body oxygen; TBK, total body potassium; TBNa, total body sodium; %, percentage of predicted normal.
Values are mean (SEM) for absolute values and mean (range) for percentage values.

(132±2/78±1).

Serum Electrolytes (Table 8.2)

Serum sodium, potassium and chloride were significantly higher in those patients with hypertension, while serum bicarbonate, urea and creatinine were higher in those with heart failure.

Hormones (Table 8.2)

Plasma concentrations of active renin, angiotensin II and aldosterone were considerably higher in subjects with heart failure. Only 2 subjects with hypertension had plasma active renin concentration above the normal range compared to 26 patients with heart failure.

Total Body Composition (Tables 8.1-8.3)

Total body potassium was depleted in subjects with heart failure, compared to normal subjects, the hypertensive group and to predicted normal values. Total body potassium was normal in the hypertensive group, as previously reported. Mean total body sodium was normal in the hypertensive group but elevated in the group with heart failure, again either by comparison with the hypertensive group or with predicted normal values. Total body chlorine was not significantly different between the 2 groups and did not deviate significantly from predicted. Although total extracellular fluid volumes was similar in hypertensives and patients with heart failure when results

were corrected for body weight, patients with heart failure had a significantly expanded volume, despite being free from clinically apparent oedema. The increase in extracellular fluid volume could account in a large part for the increase in total body sodium in the patients with heart failure.

Total body calcium tended to be higher in patients with heart failure but phosphorus was similar in both groups of patients. The ratio of phosphorus to calcium was consequently lower in the patients with heart failure.

Absolute values for total body nitrogen were similar in the heart failure group compared to normals and hypertensives. When expressed as a percentage of predicted normal, nitrogen values were increased only in the heart failure group. The difference in potassium expressed in mmol/g of nitrogen was thus highly signif icant, levels being much lower in those with heart failure. Subjects with heart failure were approximately 12% deplete of potassium compared to hypertensives, when correctd for nitrogen values.

Total body oxygen was reduced in heart failure. (Table 8.3) In the context of an expanded extracellular fluid volume, this suggests intracellular dehydration. The ratio of sodium to oxygen was increased in patients with heart failure, but the ratio of potassium to oxygen was similar

when compared to patients with hypertension.

COMPARISON OF SUB-GROUPS OF CARDIAC FAILURE PATIENTS WITH LOW OR NORMAL RENIN LEVELS AND THOSE WITH ELEVATED LEVELS (Table 8.4)

A cut-off point of 50 uU/ml for plasma active renin concentration was used, the upper limit of normal for the laboratory. Subjects in each group were well matched for anthropomorphic measurements, though the high renin group had an excess of males. The patients with high plasma renin (n=26) had correspondingly high plasma levels of angiotensin II and aldosterone. There was no difference in severity of heart failure or diuretic requirements between the groups. Total body and serum potassium, serum sodium and mean blood pressure were all inversely related to plasma renin. (Figures 8.1-8.4) Potassium supplements were significantly greater in those subjects with low serum potassium and elevated plasma renin. Extracellular fluid volume was not contracted in those with a high plasma renin.

Similar sub-setting for hypertensive patients was not carried out due to the small group (2 patients) with elevated plasma renin.

CORRELATIONS BETWEEN SERUM AND TOTAL BODY ELECTROLYTES

Table 8.4 *Comparison of measurements in patients with heart failure and with normal or high renin concentrations*

	Renin < 50 μU/ml	*Renin > 50 μU/ml*	*p*
Proportion of men to total	9/14	23/26	NS
Age (years)	58 (1)	55 (2)	NS
Height (cm)	163 (3)	168 (1)	NS
Weight (kg)	67 (3)	68 (2)	NS
NYHA	3 (2–4)	3 (2–4)	NS
Frusemide (mg/day)	124 (16)	158 (18)	NS
Bendrofluazide	2 patients	3 patients	
Potassium chloride (mg/day)	343 (0–1200)	1080 (0–2040)	< 0·05
Mean blood pressure (mm Hg)	109 (4)	87 (2)	< 0·001
Serum sodium (mmol/l)	141 (1)	137 (1)	< 0·01
Serum potassium (mmol/l)	4·0 (0·1)	3·5 (0·1)	< 0·001
Serum chloride (mmol/l)	100 (1)	97 (2)	NS
Serum bicarbonate (mmol/l)	29 (1)	29 (1)	NS
Serum urea (mmol/l)	6·2 (0·4)	6·8 (0·6)	NS
Serum creatinine (μmol/l)	101 (7)	103 (5)	NS
Urea:creatinine ratio	60 (2)	70 (2)	NS
PARC (μU/ml)	33 (4)	313 (62)	
Plasma angiotensin II (pmol/l)	20 (3)	87 (12)	< 0·001
Plasma aldosterone (pmol/l)	272 (31)	975 (160)	< 0·001
Total body potassium (%)	105 (95–117)*	91 (67–104)†	< 0·01
Total body nitrogen (%)	109 (90–133)*	104 (86–116)*	NS
Total body potassium:nitrogen (mmol:g)	1·78 (0·05)	1·63 (0·03)	< 0·01
Total body potassium:nitrogen (%)	97 (94–106)	88 (74–98)†	< 0·01
Total body sodium (%)	110 (96–129)*	106 (92–118)*	NS
Total body chlorine (%)	107 (88–142)	103 (87–120)	NS
Extracellular fluid volume (ml/kg)	260 (9)	270 (9)	NS
Total body calcium (%)	106 (86–118)	104 (83–121)*	NS
Total body phosphorus:calcium	0·54 (0·01)	0·59 (0·04)	NS
Total body oxygen (kg/kg body weight)	0·53 (0·05)	0·54 (0·08)	NS

NYHA, New York Heart Association class; %, percentage of normal predicted; PARC, plasma active renin concentration.
*p < 0·01, †p < 0·001 compared with predicted normal (see text).
Values are mean (SEM) for absolute values and mean and range for percentage values.

Serum and total body potassium (expressed as a percentage of predicted normal) were significantly correlated in patients with heart failure ($r=0.74;p<0.001$) (Figure 8.5), and this relationship was maintained after correcting total body potassium for total body nitrogen ($r=0.75;p<0.001$). The relationship appeared linear over the measured range. A similar relationship was not observed in the group with hypertension ($r=0.1;ns$ and $r=0.3;ns$). Serum sodium ($r=0.1$ heart failure and $r=0.36$ hypertension) was not significantly related to total body sodium (percentage of predicted normal) but serum chloride was related to total body chlorine (percentage of predicted normal) ($r=0.34;p<0.05$ heart failure and $r=0.59;p<0.01$ hypertension).

Figure 8.1 Relation between plasma active renin concentration (expressed on a log scale) and total body potassium (expressed as a percentage of predicted normal) in patients with heart failure. (Spearman's R=-0.51;p<0.01;n=38.

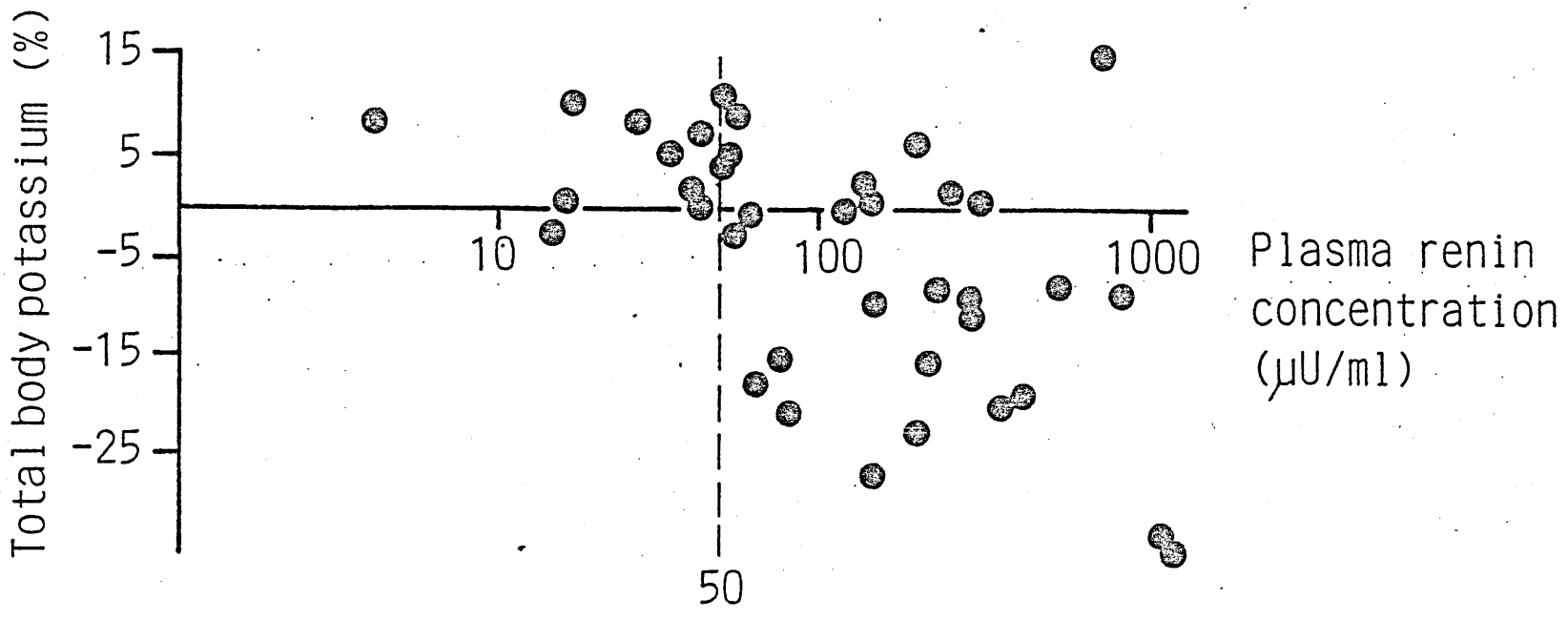


Figure 8.2 Relation between plasma active renin concentration (expressed on a log scale) and mean blood pressure in patients with heart failure. ($r=-0.76; p<0.001; n=40$)

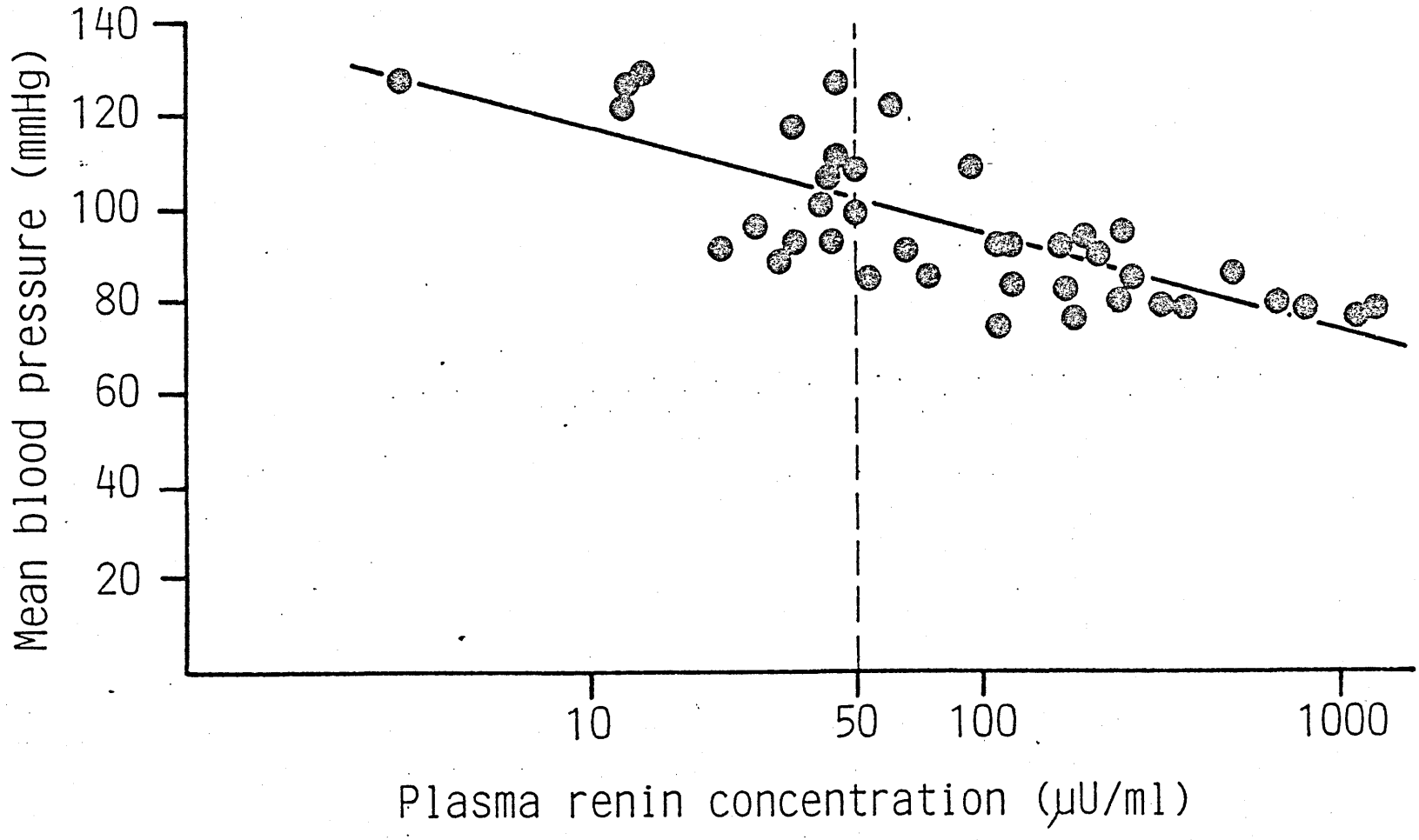


Figure 8.3 Relation between plasma active renin concentration (expressed on a log scale) and serum sodium in patients with heart failure. ($r=-0.67; p<0.001; n=40$).

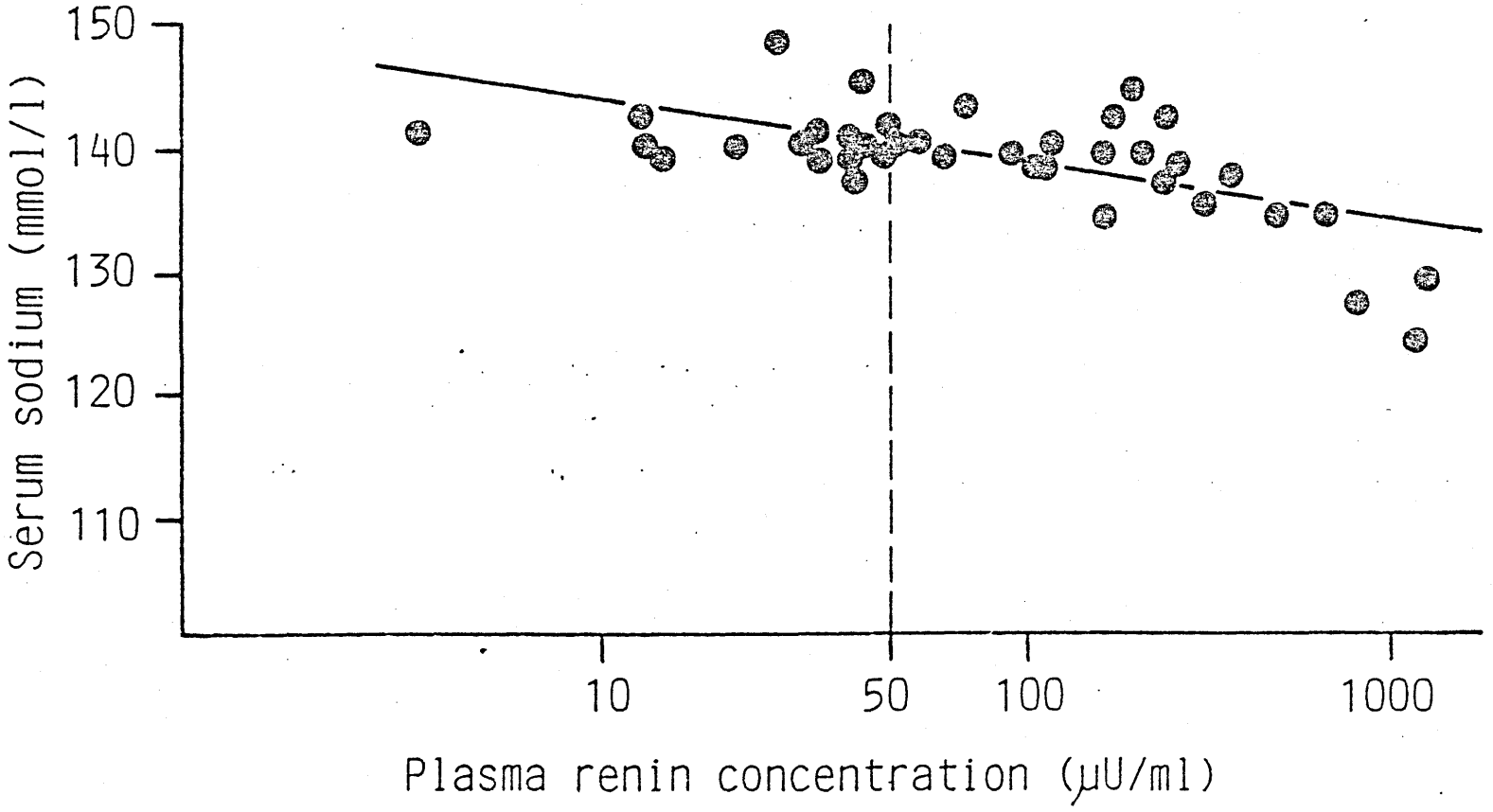
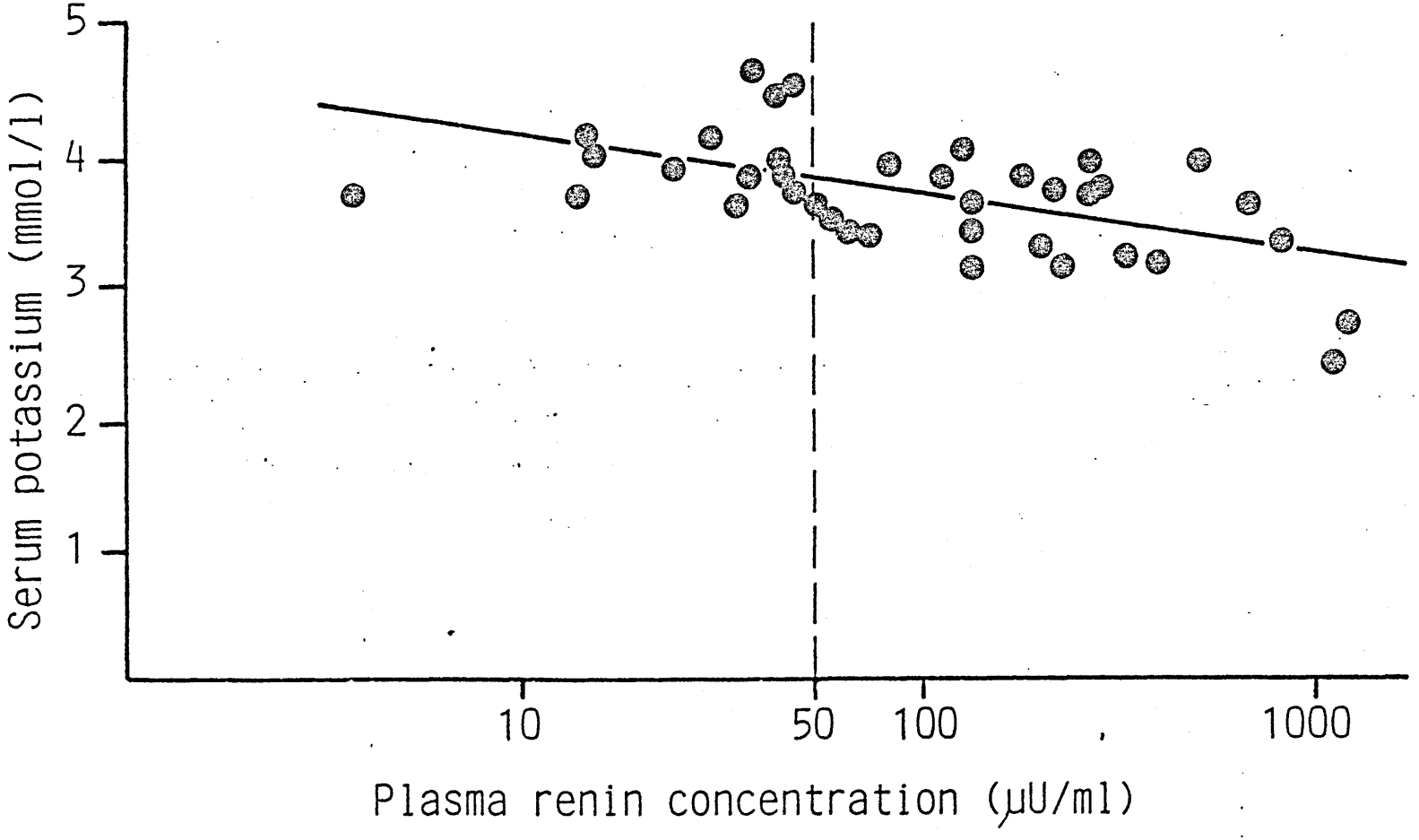


Figure 8.4 Relation between plasma active renin concentration (expressed on a log scale) and serum potassium in patients with heart failure. ($r=-0.57; p<0.001; n=40$). Two points in the central cluster of the diagram overlap and only 38 points are actually visible.



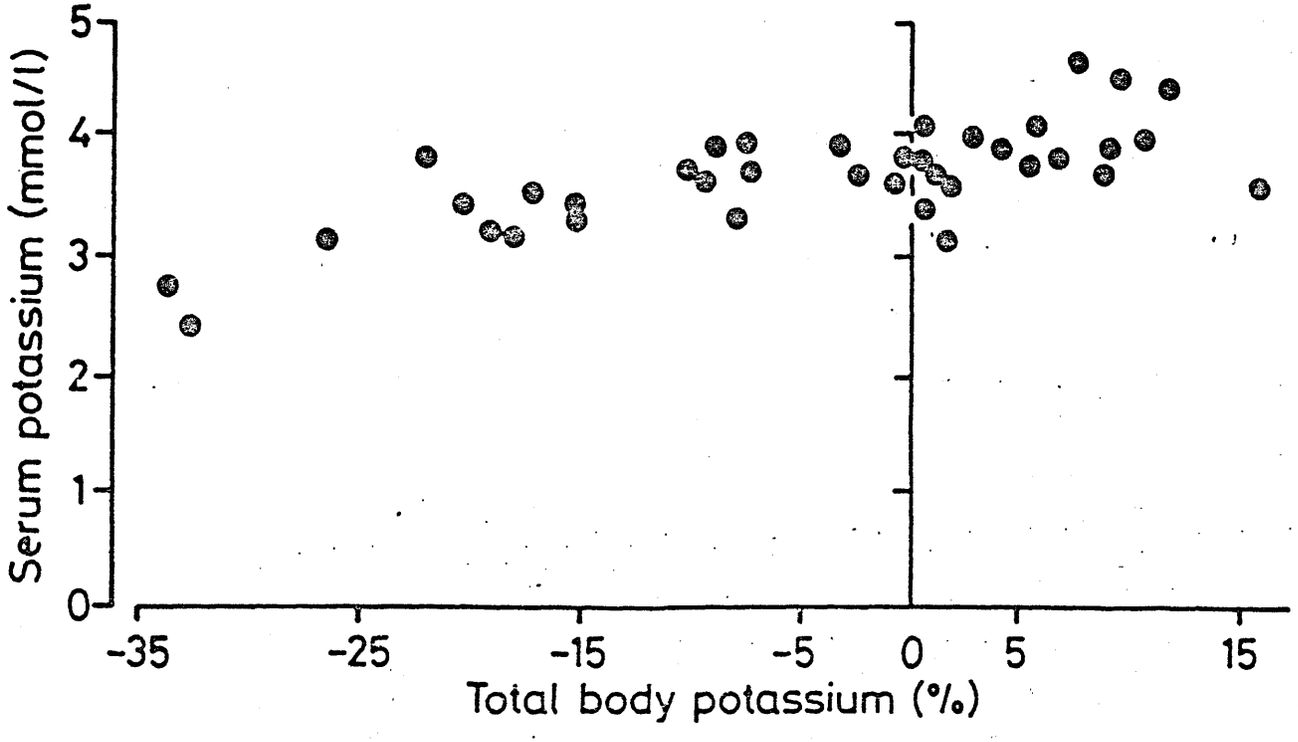


Figure 8.5 Relation between total body potassium (expressed as a percentage of predicted normal) and serum potassium in patients with heart failure. Spearman's $R=-0.72; p<0.001; n=38$).

CHAPTER 9: COMPARISON OF AUTONOMIC AND NEUROENDOCRINE FUNCTION IN NORMAL SUBJECTS AND PATIENTS TREATED FOR CHRONIC HEART FAILURE

INTRODUCTION

Peripheral circulatory control in heart failure is under the influence of both the autonomic nervous system and circulating hormones. The role of locally produced hormones and of substances such as endothelin and endothelium-dependent relaxing factor in heart failure is yet to be determined.

Although many studies have measured hormone levels and noradrenaline in the plasma, many have used historical controls or normal laboratory values from which to draw conclusions. The number of studies which have incorported an age- and sex-matched healthy control group are few. Also, there is little published information on the acute effects of diuretics on neuroendocrine activation in heart failure. While there is more information on the effects of exercise on neuroendocrine activation, there are major problems in interpreting the information as normal subjects can exercise for longer and to higher workloads. It is not clear to what extent neuroendocrine activation is dependent on duration or on the intensity of exercise.

Autonomic reflexes have been intensively investigated in

heart failure but the interpretation of the tests is open to question.

This chapter seeks to fill some of the gaps in the information on this topic and also to reassess some of the established information in preparation for later studies on the effects of angiotensin-converting enzyme inhibitors on these systems.

PATIENT SELECTION

Twenty patients with chronic heart failure due to ischaemic heart disease (9), congestive (dilated) cardiomyopathy (8) or severe left ventricular dysfunction subsequent to successful valve replacement (3) and who were in New York Heart Association Class III or IV were included. The mean age was 58±4 years and duration of symptoms at entry was 18 ±13 months. All had had symptoms for more than 3 months. Patients with serious concomitant disease or significant valvar regurgitation were excluded.

All vasodilators were withdrawn at least one month before investigation and doses of frusemide (mean daily dose 124±57 mg/day), and digoxin (mean daily dose 0.22 ±0.06 mg/day) were held constant. One patient refused frusemide and continued on bumetanide 3 mg/day. Four patients also received amiloride 10-15 mg/day, 5 potassium chloride (1.8-2.4 g/day), one hydrochlorthiazide 100 mg/day. Two patients were in atrial fibrillation, one had a ventricular

demand pacemaker, and one had been on amiodarone 400 mg/day for the previous 2 years; this continued unchanged throughout. The latter 4 patients underwent testing of neuroendocrine function but were excluded from tests of autonomic function.

Ethical supervisory committee permission was obtained for the study and written informed consent from each patient.

NORMAL SUBJECTS

Twelve age-matched normal subjects were chosen, who were on no therapy, led a sedentary life-style and who had no abnormalities detected clinically or on a 12-lead electrocardiogram. All had normal levels of serum electrolytes, urea and creatinine. Their mean age was 56 $\pm$9 years, and 9 were men.

METHODS

Patients had heart rate and blood pressure measured, and blood samples taken for the concentration of sodium, potassium, active renin, angiotensin II, aldosterone, anti-diuretic hormone, noradrenaline, and adrenaline. (See Methods) All samples were taken via an in-dwelling cannula at the following times:

1) Fasting and supine for 30 minutes between 8 and 9am.

2) Four hours after usual medication with 30 minutes supine

rest prior to sampling.

3) After 5 minutes in the upright position.

4) Immediately after exercise. Patients underwent a maximal exercise test. Normal subjects underwent 2 tests. The first test exercised them to the same level as the patients with heart failure achieved at maximal exercise. The second test was a maximal stress test but very steeply "ramped" so that exercise intensity rather than duration increased.

5) Five minutes after exercise (potassium and catecholamines only).

TESTS OF AUTONOMIC FUNCTION

Parasympathetic reflexes were tested using the Valsalva ratio, the R-R interval during deep breathing, and the 15:30 ratio immediately after standing. (See Methods)

Sympathetic reflexes were assessed using the blood pressure response to 2 minutes standing and an exercise test. (See Methods)

STATISTICAL ANALYSIS

Values were expressed as mean, median, and range where they were not normally distributed, otherwise as mean and standard deviation. Statistical evaluation was carried out in 3 ways:

1) Unpaired t-tests were used to compare actual values for patients with heart failure and normal subjects. A value $p<0.05$ is taken as significant.

2) A within-group comparison for the effects of physiological manoeuvres on clinical and neuroendocrine variables was used. For patients with heart failure a comparison was carried out for the effects of usual daily therapy on neuroendocrine and clinical variables. Non-fasting, and in the case of heart failure, post-treatment supine values were compared with values taken after 5 minutes in the upright posture. Values immediately after exercise were then compared with those obtained during upright posture. Finally, immediate post-exercise values were compared with values for potassium, noradrenaline, and adrenaline 5 minutes after exercise.

3) A between-group comparison of the magnitude of neuroendocrine and clinical changes during each of the above physiological manoeuvres was carried out.

RESULTS

Resting values for heart rate, blood pressure and neuroendocrine variables in patients with heart failure, before and after diuretic administration, and in normal subjects, are shown in Table 9.1.

At baseline, patients had a significantly lower blood pressure and higher heart rate than normal controls and exhibited marked neuroendocrine activation, with lower values for plasma sodium and potassium concentration.

In response to diuretic therapy, there was no significant change in heart rate or blood pressure. However, further marked neuroendocrine activation was observed with increases, not only in renin-angiotensin system activity, but also plasma noradrenaline. Both plasma sodium and potassium concentrations fell after diuretic therapy.

Heart rate variability during each of the tests of parasympathetic function was reduced in patients with heart failure. **(Figure 9.1)**

In response to standing, there were no marked changes in neuroendocrine activity in patients with heart failure. However, in response to standing, plasma noradrenaline rose in normal subjects. Thus, the rise in plasma noradrenaline was blunted in heart failure ($p<0.01$). **(Table 9.2)**

Blood pressure did not change significantly in either group but heart rate rose only in normal subjects, emphasizing the loss of the reflex increase in sympathetic activity with upright posture in patients with heart failure.

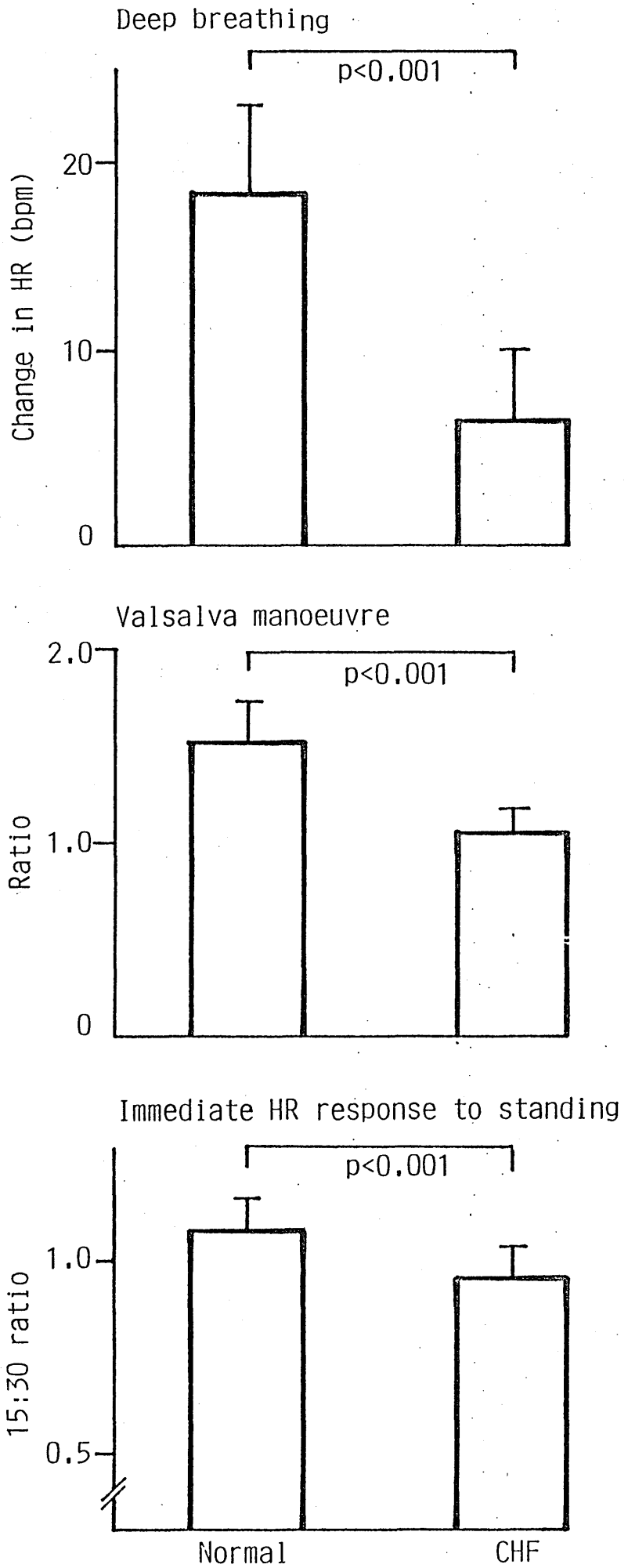


Figure 9.1 Tests of parasympathetic reflex function: a comparison of normal subjects and patients with heart failure.

HR = heart rate
CHF = congestive heart failure

TABLE 9.1

NEUROENDOCRINE EFFECTS OF DYNAMIC EXERCISE

	Patients with Heart Failure n = 20		Normal Subjects n = 12
Supine	Fasting Pre-diuretic		Non-fasting
Heart Rate (bpm)	79(10)	p<0.05	74(5)
Sys BP (mmHg)	119(26)	p<0.01	138(9)
Dia BP (mmHg)	72(11)	p<0.001	88(5)
Plasma Sodium (mmol/L)	139(3)	p<0.01	143(2)
Plasma Potassium (mmol/L)	3.8(0.3)	p<0.001	4.4(0.3)
P.A.R.C. (uU/ml)	81:47:3-352	p<0.001	14:14:6-27
P.Ang.II (pmol/L)	39:31:1-160	p<0.001	6: 6:1-17
P.Aldo. (pmol/L)	505:361:217-1336	p<0.01	224:212:36-612
P.A.D.H (pg/ml)	1.9:1.6:0.3-5.1	p<0.01	0.8:0.6:0.4-2.1
P.N.Adr (nmol/L)	3.2(1.4)	p<0.01	2.0(0.8)
P.Adr (nmol/L)	0.3(0.1)	ns	0.2(0.1)

	Non-fasting Post-diuretic	significance v. pre-diuretic	significance v. normals
Heart Rate (bpm)	83(12)	ns	p<0.01
Sys BP (mmHg)	122(24)	ns	p<0.01
Dia BP (mmHg)	77(18)	ns	p<0.01
Plasma Sodium (mmol/L)	138(3)	p<0.01	p<0.001
Plasma Potassium (mmol/L)	3.5(0.3)	p<0.001	p<0.001
P.A.R.C. (uU/ml)	152:91:3-972	p<0.001	p<0.001
P.AngII (pmol/L)	55:46:0.5-134	p<0.01	p<0.001
P.Aldo. (pmol/L)	650:469:108-1949	p<0.01	p<0.001
P.A.D.H. (pg/ml)	2.2:1.9:0.3-5.9	ns	p<0.001
P.Noradr. (nmol/L)	3.9(1.4)	p<0.001	p<0.001
P.Adr. (nmol/L)	0.4(0.2)	ns	p<0.05

Figures are given as mean (S.D.) or mean:median:range
P. = plasma. SYS = systolic. DIA = diastolic
A.R.C. = active renin concentration. Aldo = aldosterone.
Ang II = angiotensin II. A.D.H. = anti-diuretic hormone.
Adr = adrenaline

TABLE 9.2

NEUROENDOCRINE EFFECTS OF DYNAMIC EXERCISE

		Patients with Heart Failure n = 20			Normal Subjects n = 12	
Upright Pre-exercise						
Heart Rate (bpm)		82(14)	ns	*	80(6)	@@
Sys BP (mmHg)		116(20)	p<0.005		138(12)	
Plasma Potassium (mmol/L)		3.5(0.3)	p<0.001		4.6(0.5)	
Plasma Sodium (mmol/L)		138(3)	p<0.001		143(3)	
P.A.R.C. (uU/ml)		183:103:4-1356	p<0.001		18:18:6-38	
P.Ang.II (pmol/L)		54: 40:7-156	p<0.001		9: 7:3-20	
P.Aldo. (pmol/L)		686:505:108-2527	p<0.001		291:289:72-694	
P.A.D.H (pg/ml)		2.2:2.1:0.3-6.5	p<0.001		1.1:0.9:0.4-2.6	
P.N.Adr (nmol/L)		4.1(1.5)	p<0.001	**	2.8(0.8)	@@
P.Adr (nmol/L)		0.3(0.3)	ns		0.3(0.1)	
Upright Immediate Post-exercise					(Light Exercise)	
Time (minutes)		6.5(3.2)	ns		6.5	
Heart Rate (bpm)	**	121(17)	p<0.01	**	107(12)	@@
Sys BP (mmHg)	**	145(27)	p<0.01	**	165(23)	
Plasma Potassium (mmol/L)	**	3.9(0.3)	p<0.01	**	4.9(0.8)	
Plasma Sodium (mmol/L)	*	139(3)	p<0.001		143(5)	
P.A.R.C. (uU/ml)	**	219:183:4-1443	p<0.001		21: 18:6-50	@@
P.AngII (pmol/L)	**	81: 57:10-183	p<0.001		10: 9:2-26	@@
P.Aldo. (pmol/L)	**	975:578:289-3032	p<0.001		357:288:36-1152	@@
P.A.D.H. (pg/ml)	**	7.5:3.4:0.5-57	p<0.001		1.4:1.4:0.4-2.8	@@
P.N.Adr (nmol/L)	**	8.4(4.0)	p<0.02	*	6.1(3.2)	
P.Adr (nmol/L)	*	0.5(0.5)	ns	*	0.5(0.3)	
Five Minutes Post-exercise						
Plasma Potassium (mmol/L)	**	3.2(0.5)	p<0.001		4.5(0.7)	@@
P.N.Adr (nmol/L)		7.4(4.6)	p<0.001	*	3.6(1.1)	@@
P.Adr (nmol/L)		0.7(0.6)	p<0.05		0.3(0.2)	@

Comparisons have been made in three ways (see text for details):-
1) The actual values of normal subjects and patients with heart failure These values are given in the central column
2) * indicates a within group comparison of the effects of physiological manouevres. * = p<0.05, ** = p<0.01.
3) @ indicates between group comparisons. @ = p<0.05, @@ = p<0.01

For abbreviations see table 9.1

During exercise, further marked increases in neuroendocrine activation were observed in patients with heart failure. At the same work intensity, patients with heart failure had a similar blood pressure response but an exaggerated heart rate response compared to normal subjects. In normal subjects the renin- angiotensin-aldosterone system and anti-diuretic hormone showed little evidence of activation at this workload. Plasma noradrenaline was less in normal subjects in absolute terms compared to patients with heart failure during this form of exercise, but the magnitude of increase was similar. **(Table 9.2)**

In contrast, normal subjects had marked increases in anti-diuretic hormone and catecholamines during maximal exertion, several times that seen in patients with heart failure. **(Table 9.3)** The plasma levels of renin, angiotensin II and aldosterone achieved at maximal exertion were still significantly less in patients with heart failure. Although the magnitude of the change from the resting state was similar in patients with heart failure compared to normal subjects, when considered as a percentage of the basal levels, then the increases in renin-angiotensin system activity during maximal exertion was greater in normal subjects than in patients with heart failure.

Potassium rose during exercise in each group of subjects.

TABLE 9.3

NEUROENDOCRINE EFFECTS OF DYNAMIC EXERCISE

		Patients with Heart Failure			Normal Subjects	
		n = 20			n = 12	
Upright Immediate Post-exercise				(Strenuous Exercise)		
Time (minutes)		6.5(3.2)	ns		6.7(1.2)	
Heart Rate (bpm)	**	121(17)	p<0.001	**	174(15)	@@
Sys BP (mmHg)	**	145(27)	p<0.001	**	194(17)	@@
Plasma Potassium (mmol/L)	**	3.9(0.3)	p<0.001	**	5.7(0.9)	@@
P.A.R.C. (uU/ml)	**	219:183:4-1443	p<0.01	**	64:52:9-161	@
P.AngII (pmol/L)	**	81: 57:10-183	p<0.01	**	29: 21:2-67	
P.Aldo. (pmol/L)	**	975:578:289-3032	p<0.05	**	690:478:128-1764	
P.A.D.H. (pg/ml)	**	7.5:3.4:0.5-57	p<0.01	**	21.3:16.3:1.1-62.9	@@
P.N.Adr (nmol/L)	**	8.4(4.0)	p<0.001	**	30.4(12.9)	@@
P.Adr (nmol/L)	*	0.5(0.5)	p<0.01	**	2.5(1.3)	@@
Five Minutes Post-exercise						
Plasma Potassium (mmol/L)	**	3.2(0.5)	p<0.001	**	4.1(0.8)	@@
P.N.Adr (nmol/L)		7.4(4.6)	p<0.001	**	5.9(2.7)	@@
P.Adr (nmol/L)		0.7(0.7)	P<0.05		0.4(0.9)	@@

Comparisons are made in three ways (see text for details):-

1) The actual values of normal subjects and patients (p values given in central column)
2) * indicates a within group comparison of the effects of physiological manoeuvres (in this case a comparison between the the supine non-fasting state and immediate post-exercise values or immediate and 5 minute post-exercise values). * = p<0.05, ** = p<0.01.
3) @ indicates between group comparisons. @ = p<0.05, @@ = p<0.01.

For abbreviations see table 9.1

The rise in potassium in patients with heart failure was similar to that seen during light exercise in normal subjects. The rise in potassium during strenuous exercise was considerably greater in normal subjects compared to maximal exercise in patients with heart failure. **(Tables 9.2 & 9.3)**

Five minutes after exertion, plasma noradrenaline and adrenaline remained markedly elevated in the heart failure group while plasma potassium had fallen below resting baseline levels ($p<0.05$). In contrast, in normal subjects, plasma noradrenaline had fallen to near baseline levels 5 minutes after light exercise, while plasma potassium had also returned to normal. Five minutes after strenuous exercise in normal subjects, plasma noradrenaline levels had dropped considerably but not to normal levels. Post-exercise serum potassium was still within the normal range but was significantly ($p<0.05$) lower than resting baseline levels.

CHAPTER 10: RELATION OF ARRHYTHMIAS, ELECTROLYTE AND NEUROENDOCRINE ABNORMALITIES TO SURVIVAL IN PATIENTS WITH SEVERE CHRONIC HEART FAILURE

INTRODUCTION

Although the conventional treatment of heart failure with potent diuretic drugs has improved the symptoms and the short-term outlook of patients with congestive heart failure, the long-term prognosis in patients with severe left ventricular dysfunction referred to tertiary care centres remains extremely poor.[669-673] Diuretics act to correct the abnormal sodium retention seen in patients with heart failure,[674,675] but they also stimulate the renin-angiotensin system, which is already activated in these patients as a result of compromised renal perfusion.[676,677] Unfortunately, such neurohormonal activation may lead to important electrolyte abnormalities, particularly hyponatraemia and hypokalaemia.These adverse metabolic effects may have their own prognostic consequences[678] or may be associated with an increased frequency of serious ventricular arrhythmias.[679-682]

The arrhythmogenic potential of diuretic therapy in patients with congestive heart failure may have important clinical implications. When evaluated by the physician, most patients with congestive heart failure show a high frequency of ventricular ectopic activity on ambulatory electrocardiographic monitoring,[671,673,683,684] and many die

suddenly during long-term follow-up. [669-671]

It has been demonstrated in previous chapters that there are serious electrolyte abnormalities in patients with heart failure, and that this may be related to neuroendocrine activation. Therefore, we evaluated the relative importance of a number of potential prognostic factors (including hyponatraemia and hypokalaemia) in a prospective study of patients with congestive heart failure secondary to left ventricular dysfunction, in whom we investigated the relationship among electrolyte abnormalities, ventricular function, ventricular arrhythmias, and neuroendocrine activation.

PATIENTS

The study population comprised 84 consecutive patients in whom a diagnosis of heart failure of greater than 3 months' duration was established and in whom measurements of plasma active renin and noradrenaline concentrations were made. In each patient the diagnosis of congestive heart failure was confirmed by a typical clinical presentation, supported by objective evidence of left ventricular dysfunction by echocardiography.All patients had a left ventricular end-diastolic dimension greater than 58 mm and a cardiothoracic ratio (on a posteroanterior chest X-ray) greater than 0.52.All patients had symptoms of dyspnoea or fatigue at rest or on exertion but were symptomatically stable. The functional status (New York Heart Association

Class) of these patients was Class II in 27 patients, Class III in 31 patients, and Class IV in 26 patients. There were 66 men and 18 women, ranging in age from 22 to 78 years (mean 59). The median duration of heart failure was 20 months (range 12-82).

The cause of heart failure in these patients was ischaemic heart disease in 48 patients, idiopathic dilated cardiomyopathy in 20, residual left ventricular dysfunction after successful valve replacement in 10, previous hypertension in 2, and alcohol-related cardiomyopathy in 4. Patients in whom angina was a significant complaint at rest or during exercise were excluded from this study. Coronary artery disease was diagnosed either by coronary angiography or by a typical history of myocardial infarction supported by appropriate electrocardiographic and enzymatic changes.Idiopathic dilated cardiomyopathy was diagnosed on the basis of angiographically normal coronary arteries and the absence of any specific heart muscle disease as determined by endomyocardial biopsy. All patients were stabilised on diuretics (frusemide 40-750 mg/day;mean 143), and in most cases (68 patients) digoxin for at least one month before entry into this study. No patient was taking a potassium-sparing diuretic, but 23 patients were taking potassium chloride supplements (median dose 1800 mg/day; range 600-2400). All patients were evaluated at a time of clinical compensation, and were not receiving vasodilator or anti-arrhythmic therapy.

METHODS

BASELINE EVALUATION

All patients underwent the following tests within one week:

1) Vital signs, including heart rate and blood pressure. These measurements were made on at least 3 occasions and at different times of the day, and an average of 3 values was used for analysis.

2) Treadmill exercise test, using a modified Bruce protocol. All patients had had at least one previous exercise test with the same protocol, and all tests were carried out by the same cardiologist and technician. All tests were symptom-limited and were stopped in all cases because of breathlessness or fatigue.

3) Ambulatory electrocardiographic monitoring using a Medilog I system, with subsequent analysis using a Pathfinder Analyzer under constant visual monitoring. The median duration of ambulatory monitoring was 72 hours (range 48-120).

4) M-mode echocardiography under 2-dimensional control with each patient in the left lateral position.

5) Serum sodium and serum potassium concentrations, analysed from venous blood samples taken on at least 2 occasions at different times of the day (average value used

for analysis); the median number of samples was 5 (range 2-10). Potassium-sparing diuretics had been withdrawn for at least 2 weeks before these measurements, but potassium supplements were continued if the patient had been receiving these previously.

6) Serum digoxin concentration, analysed from blood drawn at least 6 hours after the last dose of the drug.

7) Total body sodium (measured by activation analysis) and total body potassium (measured by endogenous levels of ^{40}K); values for both variables were expressed as a percentage of predicted normal on the basis of age, sex, height and weight.[685,686]

8) Plasma active renin (by radio-immunoassay) and plasma noradrenaline (by radio-enzymatic assay).[687,688]

DRUG TREATMENT

After the completion of these baseline evaluations, 51 patients were treated with an angiotensin-converting enzyme inhibitor, either captopril or enalapril. The median maintenance dose of captopril was 75 mg/day (range 37.5-150) and that of enalapril was 10 mg/day (range 5-40). Twenty-nine patients were treated with amiodarone, initially at a dose of 200 mg, 3 times/day, followed by a mean daily maintenance dose of 183±54 mg (range 100-400).

Patients were allocated to treatment with converting-enzyme inhibitors or amiodarone either for clinical reasons according to the preference of the attending physician, or in the context of a clinical trial. Patients received no other vasodilator drugs or anti-arrhythmic agents unless otherwise stated.

DATA ANALYSIS

The mode of death was ascertained from the patient's relatives, the patient's physician, or the hospital staff. When death was believed to be due to cardiac causes, it was classified as sudden or the result of pulmonary oedema or cardiogenic shock. Sudden death was defined as death occurring without a marked change in symptoms in the preceding 24 hours. In those patients who died suddenly, further inquiries were made to determine whether they experienced some gradual deterioration in their symptoms of heart failure in the month before death.

The log-rank test was used to compare the survival rates among designated therapeutic subgroups. Predictors of mortality were determined by a Cox proportional hazards model, which identifies and corrects for important co-variates.[689] Both forward and backward elimination procedures were carried out to protect against the omission of important predictors.[690] Kaplan-Meier survival curves were constructed, where appropriate. Pearson's product-moment correlation coefficients were calculated to investigate

potential inter-relationships among prognostic variables. Group means are presented as mean±SD unless stated otherwise.

RESULTS

Baseline Characteristics of Patients

The initial mean arterial pressure in our patients was 91±14 mm Hg (range 66-130). The mean serum sodium concentration was 137±6 mmol/l (range 124-148), and the mean serum potassium concentration was 3.7±0.4 mmol/l (range 3.0-4.6). Total body potassium was reduced at 96±10% of predicted normal ($p<0.05$), and total body sodium was increased at 107±9% of predicted normal ($p<.01$). The mean plasma concentrations of active renin and noradrenaline were elevated, 227±357 U/l (range 4- 1705) and 4.8±3.1 nmol/l (range 1.0-18.4), respectively. The mean end-diastolic and end-systolic left ventricular dimensions were 68±8 and 58±10 mm, respectively; the mean percent fractional shortening was 15.0±6.8%.

The mean frequency of ventricular extrasystoles was 5181/24 hours (median=1837;range:0-24,299). Couplets or salvoes of ventricular extrasystoles were found in 82% of patients during the course of ambulatory monitoring (mean 17/24 hours;median=11;range 0-768). Ventricular tachycardia was seen in 61% of patients, with a mean overall frequency of 8 events/24 hours (median=2:range:0-201). The frequency of ventricular extrasystoles and ventricular tachycardia was

related (r=0.67;p<.001).

Patients treated with amiodarone were similar to those who did not receive the drug with respect to all pre- treatment variables. **(Table 10.1)** Patients treated with converting-enzyme inhibitors were similar to those who were not, except that patients who received captopril or enalapril received larger doses of frusemide (165±16 mg/day) and had higher plasma active renin concentrations (275±385 U/ml) than those who did not (108±52 mg/day;p<.01;153±300 U/ml;p<0.05, respectively).(Table 10.2).

PROGNOSTIC VARIABLES

The mean duration of follow-up was 31 months (range 12-52), during which time 49 patients (58%) died. Of these deaths, 35 were sudden (71%), and although clinical deterioration had occurred in 8 patients in the preceding months, death in these patients was nonetheless unexpected. Five patients died in cardiogenic shock after a recurrent myocardial infarction, and 2 died after a cerebrovascular accident.One patient died after a mesenteric artery occlusion, one postoperatively after peripheral vascular surgery, one from chronic lymphatic leukaemia and associated respiratory infections, and one from rectal carcinoma.Only 3 deaths were considered to be the result of intractable heart failure. Four patients who died suddenly had developed symptomatic sustained ventricular tachycardia

Table 10.1

Pretreatment clinical, biochemical, and hemodynamic variables in patients grouped according to treatment with amiodarone

	Amiodarone (n = 29)	No Amiodarone (n = 55)	p value
Age (yr)	59 ± 8 (39–75)	58 ± 7 (31–72)	NS
Cause of heart failure			
Coronary artery disease	20	28	NS
Idiopathic cardiomyopathy	27	9	NS
Duration of heart failure (mo)	21 ± 20 (3–84)	19 ± 18 (3–72)	NS
Mean arterial pressure (mm Hg)	93 ± 13 (67–126)	89 ± 15 (66–124)	NS
Fractional shortening (%)	14.5 ± 6.0 (6.4–30.0)	15.0 ± 7.0 (4.0–30.0)	NS
Exercise time (min)	7.4 ± 5.0 (0.4–14)	6.5 ± 5.0 (0.4–16)	NS
Furosemide dose (mg/day)	130 ± 60 (40–250)	150 ± 113 (40–750)	NS
Ventricular extrasystoles (per 24 hr)	1705 (10–16742)	1860 (56–24299)	NS
Plasma active renin concentration (μU/ml)	272 ± 390 (14–1705)	203 ± 340 (4–1467)	NS
Plasma norepinephrine (nmol/l)	4.9 ± 3.5 (1.7–13.7)	4.6 ± 2.9 (1.0–18.0)	NS
Serum sodium concentration (mmol/l)	136.6 ± 4.0 (128–143)	136.7 ± 6.2 (124–148)	NS
Serum potassium concentration (mmol/l)	3.7 ± 0.3 (3.2–4.3)	3.8 ± 0.4 (3.0–4.6)	NS
Total body sodium (percent predicted normal)	105 ± 9 (95–125)	108 ± 9 (95–129)	NS
Total body potassium (percent predicted normal)	98 ± 9 (74–117)	95 ± 13 (67–113)	NS

Values shown represent mean, SD, and range within each group.

Table 10.2

Pretreatment clinical, biochemical, and hemodynamic variables in patients grouped according to treatment with converting-enzyme inhibitors

	Converting-enzyme inhibitor (n = 51)	No converting-enzyme inhibitor (n = 33)	p value
Age (yr)	58 ± 8 (31–75)	58 ± 8 (39–73)	NS
Cause of heart failure			
Coronary artery disease	27	21	NS
Idiopathic cardiomyopathy	24	12	NS
Duration of heart failure (mo)	18 ± 18 (3–72)	22 ± 22 (3–84)	NS
Mean arterial pressure (mm Hg)	88 ± 13 (67–122)	94 ± 15 (67–126)	NS
Fractional shortening (%)	14.7 ± 6.5 (5.0–32.8)	15.3 ± 7.0 (4.0–30.0)	NS
Exercise time (min)	6.6 ± 4.0 (0.4–16)	7.0 ± 4.0 (0.4–16)	NS
Furosemide dose (mg/day)	165 ± 113 (40–750)	108 ± 53 (40–200)	< .01
Ventricular extrasystoles (per 24 hr)	2106 (13–24299)	1420 (10–16742)	NS
Plasma active renin concentration (μU/ml)	275 ± 385 (4–1467)	153 ± 300 (5–1705)	< .05
Plasma norepinephrine (nmol/l)	4.9 ± 3.2 (1.0–18.4)	4.6 ± 3.0 (1.0–13.7)	NS
Serum sodium concentration (mmol/l)	135.9 ± 5.8 (124–138)	137.9 ± 4.8 (128–138)	NS
Serum potassium concentration (mmol/l)	3.6 ± 0.3 (3.0–4.3)	3.9 ± 0.4 (3.2–4.6)	NS
Total body sodium (percent predicted normal)	107 ± 10 (95–129)	106 ± 7 (100–120)	NS
Total body potassium (percent predicted normal)	96 ± 12 (67–113)	98 ± 13 (74–117)	NS

Values shown represent mean, SD, and range within each group.

Table 10.3

Univariate analysis of factors related to survival

Variable	χ^2	p value
Ventricular extrasystoles	20.9	.00001
Exercise time	17.8	.00001
Mean arterial pressure	13.0	.001
Serum sodium concentration	12.1	.001
Plasma norepinephrine	12.0	.001
Amiodarone	9.9	.01
Plasma active renin concentration	9.6	.01
Fractional shortening	8.3	.01
Serum potassium concentration	7.6	.01

during follow-up. None had been on anti- arrhythmic therapy at the time, although each subsequently received treatment with procainamide (2 patients), tocainide (one patient), or amiodarone (one patient).

Using a Cox proportional hazards model and taking each variable separately, several variables were found to be of prognostic value (in order of importance): ventricular extrasystoles, exercise time, mean arterial pressure, serum sodium concentration, plasma noradrenaline concentration, therapy with amiodarone, plasma active renin concentration, fractional shortening, and serum potassium concentration. **(Table 10.3 and Figures 10.1-10.8)** Using stepwise regression analysis, 5 variables had independent prognostic significance: ventricular extrasytoles, fractional shortening, a diagnosis of coronary heart disease, exercise time, and treatment with amiodarone. **(Figures 10.1-10.8)** No predictive value of ventricular tachycardia independent of ventricular extrasystoles was observed.

RELATIONSHIPS AMONG PROGNOSTIC VARIABLES

The frequency of ventricular extrasystoles varied directly with plasma concentrations of active renin ($r=0.45$) and noradrenaline ($r=0.52$) and inversely with exercise time ($r=-0.46$), mean arterial pressure ($r=-.46$), serum sodium concentration ($r=-.44$), and serum potassium concentration ($r=-0.44$); all $p<.001$). **(Fig 10.9)** No association was seen with either the use of digoxin or with serum digoxin levels

Figure 10.1 Cumulative proportion surviving

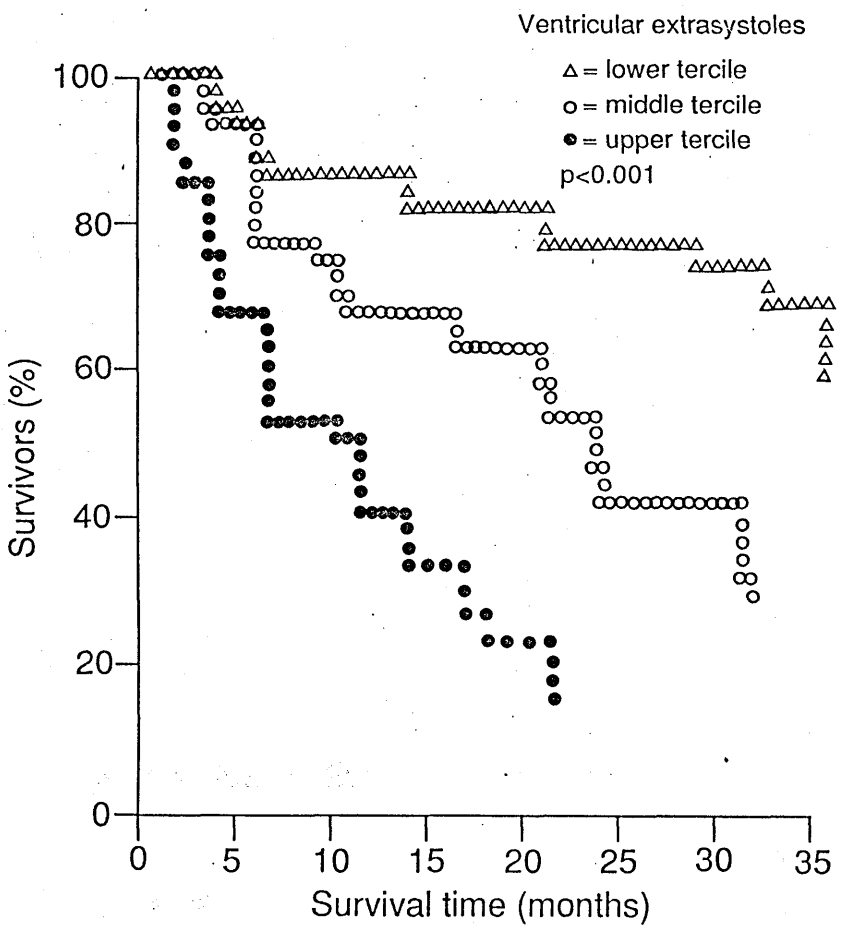


Figure 10.2 Cumulative Proportion Surviving

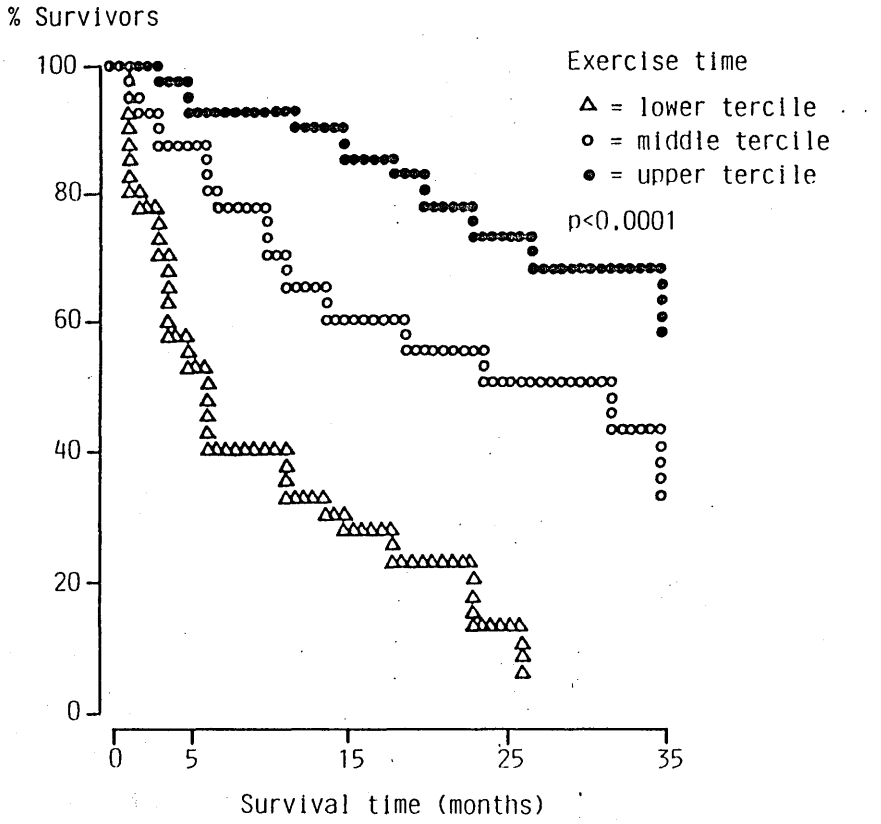


Figure 10.3 Cumulative Proportion Surviving

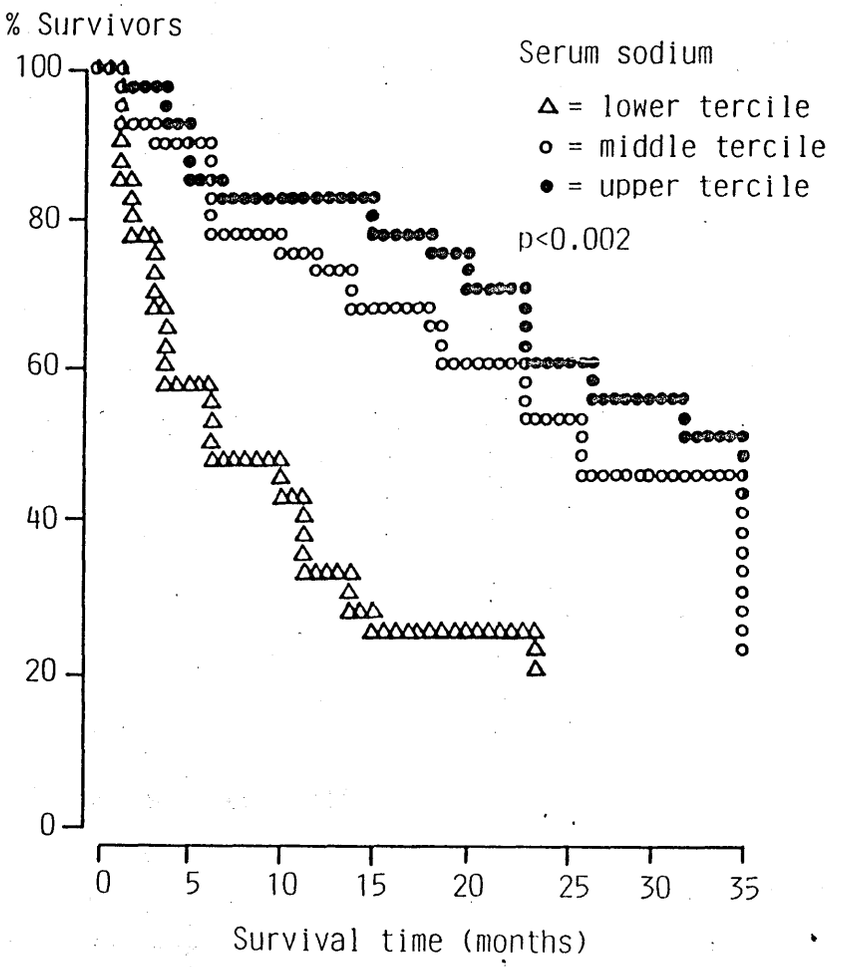


Figure 10.4 Cumulative Proportion Surviving

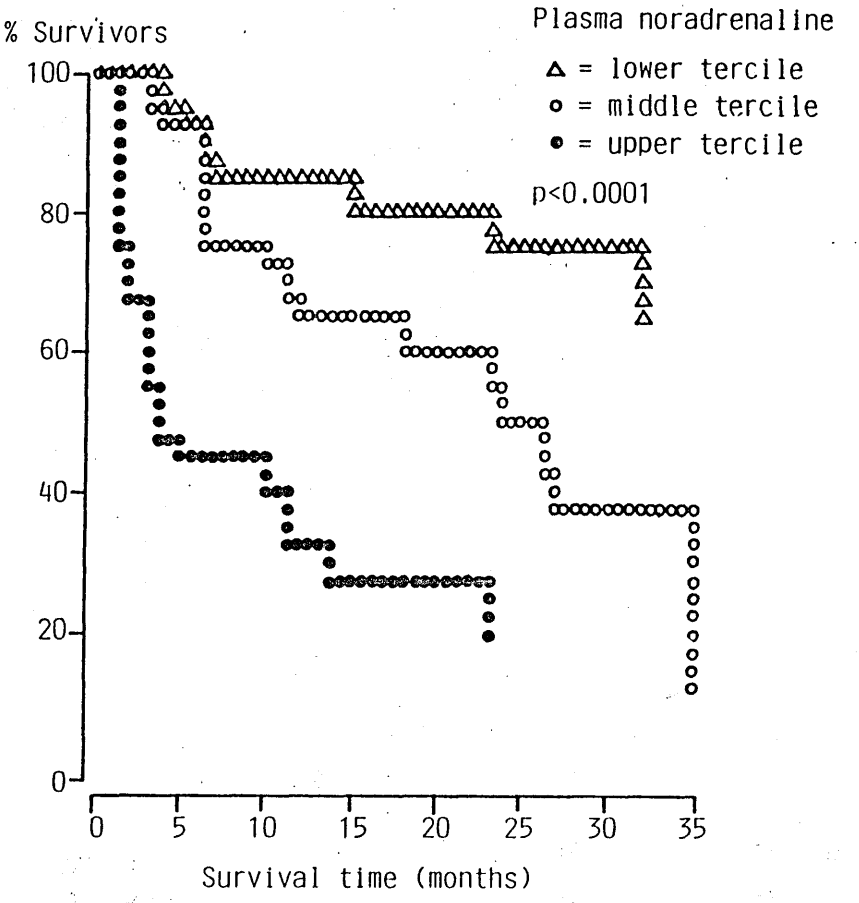


Figure 10.5 Cumulative Proportion Surviving

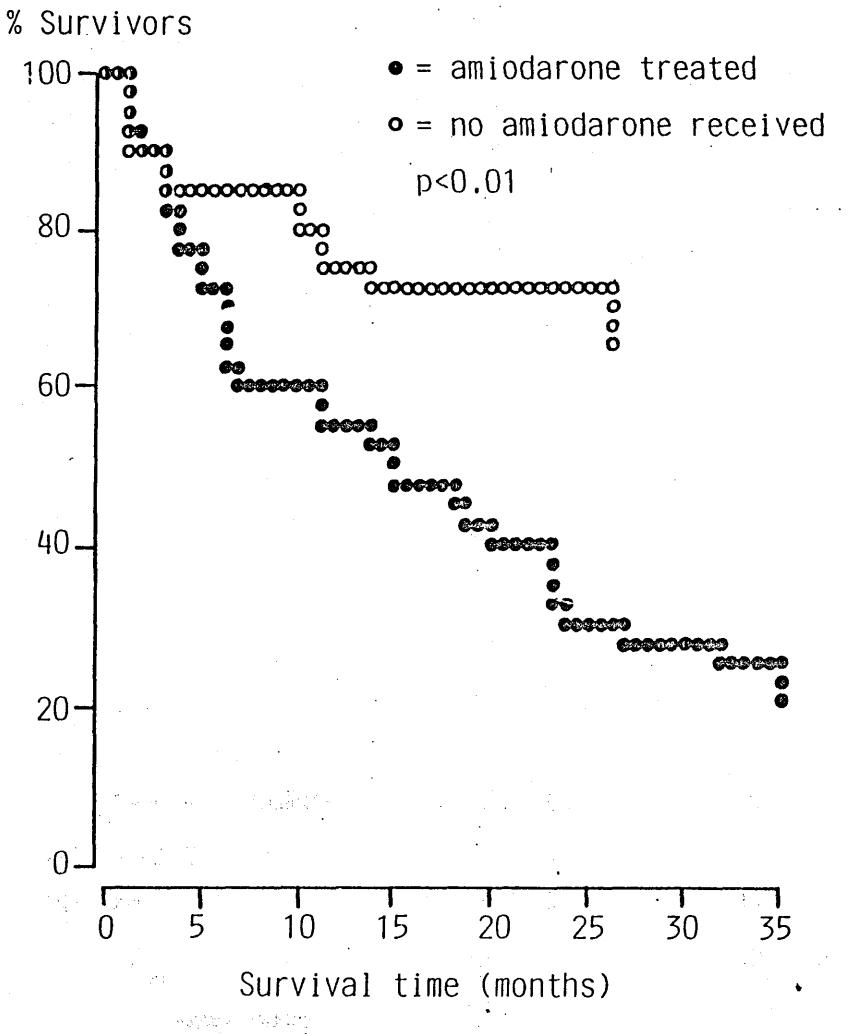


Figure 10.6 Cumulative Proportion Surviving

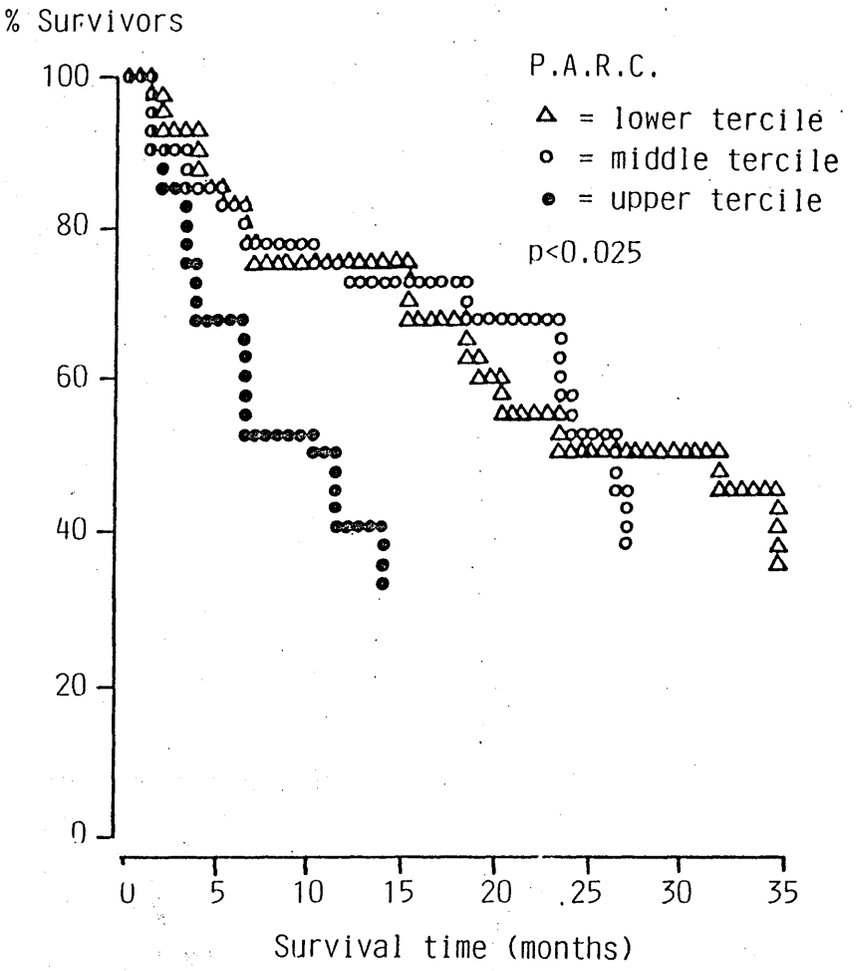


Figure 10.7 Cumulative Proportion Surviving

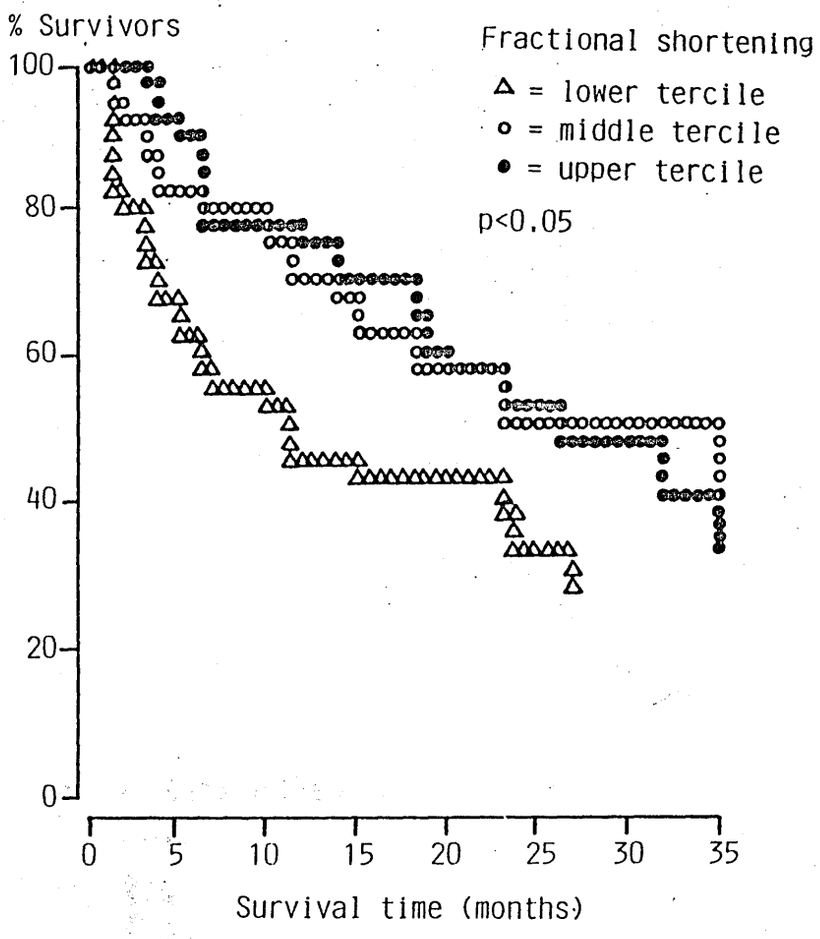
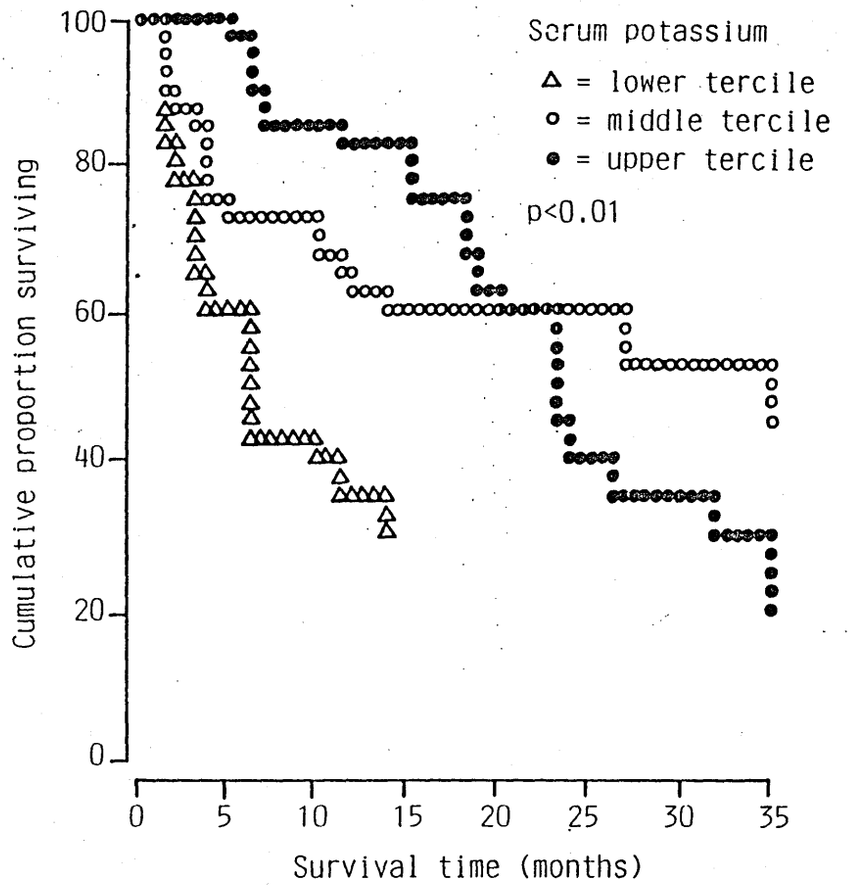


Figure 10.8 Cumulative Proportion Surviving



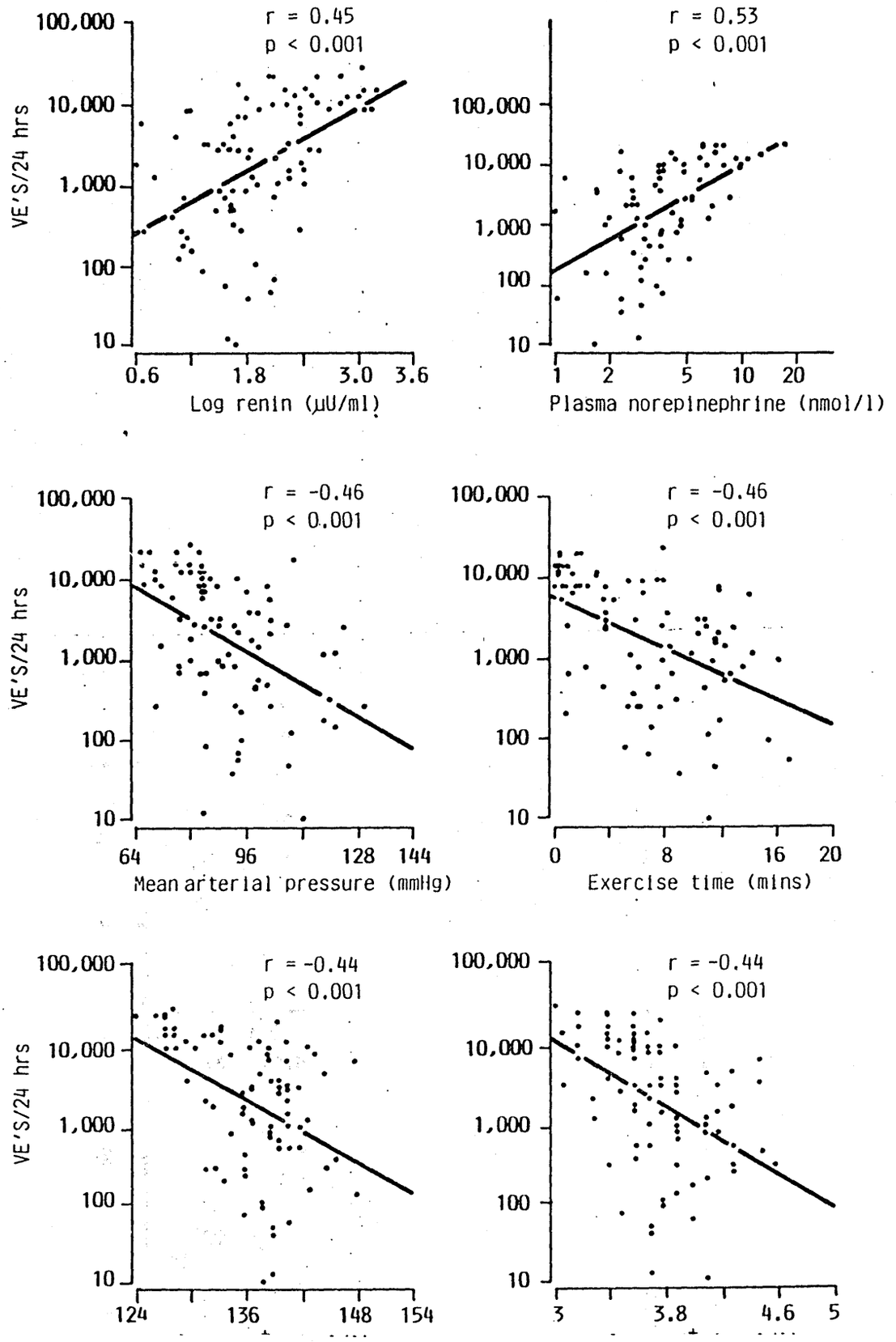


Figure 10.9 Correlation plots showing relationship between ventricular ectopic activity (VES/24 hr) and pretreatment values for plasma active renin concentration, plasma norepinephrine, mean arterial pressure, exercise time, serum sodium (Na^+) concentration, and serum potassium (K^+) concentration in patients with congestive heart failure.

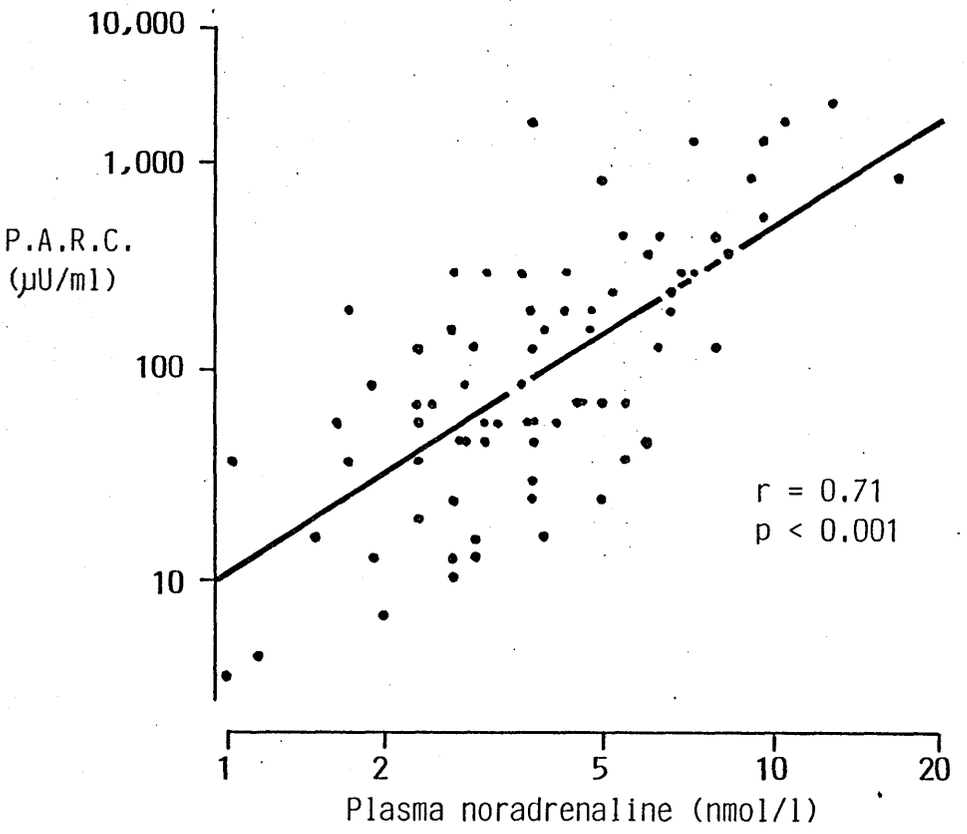

10,000
1,000
100
10
P.A.R.C.
(μU/ml)
r = 0.71
p < 0.001
1
2
5
10
20
Plasma noradrenaline (nmol/l)

Figure 10.10

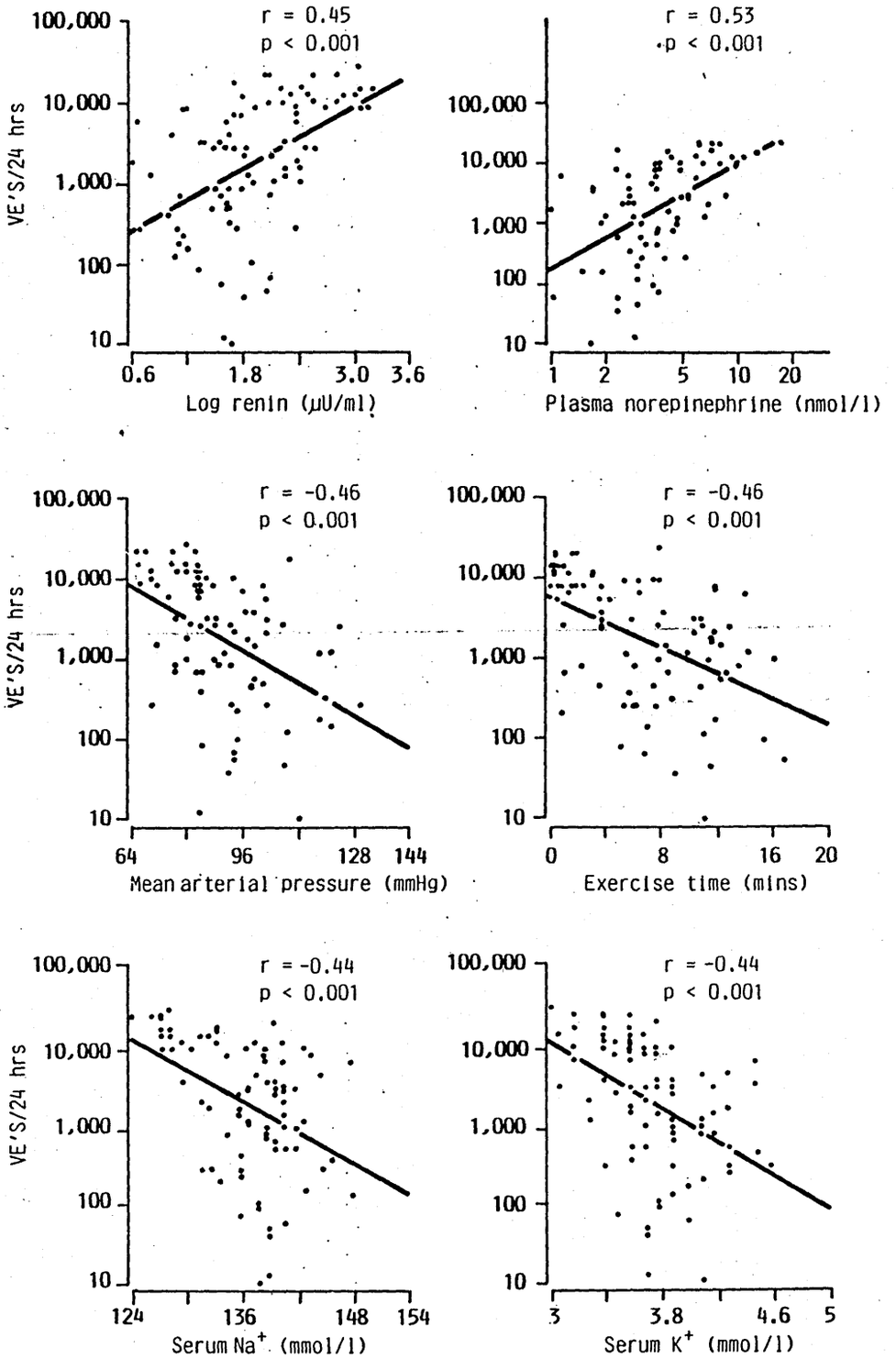


Figure 10.9 Correlation plots showing relationship between ventricular ectopic activity (VES/24 hr) and pretreatment values for plasma active renin concentration, plasma norepinephrine, mean arterial pressure, exercise time, serum sodium (Na^+) concentration, and serum potassium (K^+) concentration in patients with congestive heart failure.

(range 0.8-2.3 nmol/l). Of the associations noted above, only plasma noradrenaline and exercise time were independently related to the frequency of ventricular extrasystoles, but these two variables explained only 35% of the observed variability (R^2 value).

The percent fractional shortening was weakly and inversely related to mean arterial pressure (r=- 0.23;p<.05) but was not significantly related to any other variable, including the frequency of ventricular extrasystoles.

Exercise time was linearly and inversely related to plasma active renin concentration 0(r=-.35;p<.01) and plasma noradrenaline (r=-0.51;p<.001) but was linearly and directly related to mean arterial pressure (r=0.48;p<.001).

Plasma active renin concentration varied linearly and directly with plasma noradrenaline (r=-0.71). **(Figure 10.10)** Plasma renin and noradrenaline were inversely related to serum potassium concentration (r=-0.53 and -0.47, respectively), serum sodium concentration (both r=-0.62), mean arterial pressure (r=-0.50 and -0.52, respectively) and exercise time (r=-0.35 and -0.53).**(Figure 10.11)**By multiple regression analysis, the combination of serum potassium concentration, plasma noradrenaline, age, and mean arterial pressure carried independent information accounting for 75% (R^2 value) of the observed variation in log plasma active renin.The severity of heart failure (as

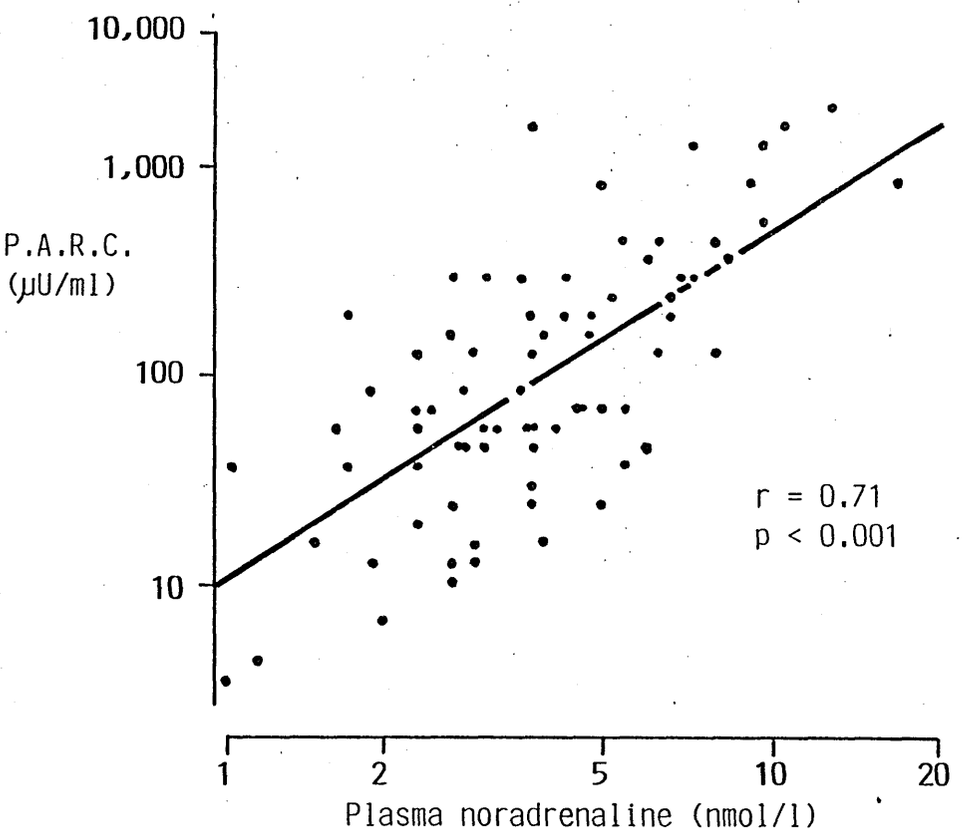

10,000
1,000
100
10
P.A.R.C.
(μU/ml)
r = 0.71
p < 0.001
1
2
5
10
20
Plasma noradrenaline (nmol/l)

Figure 10.10

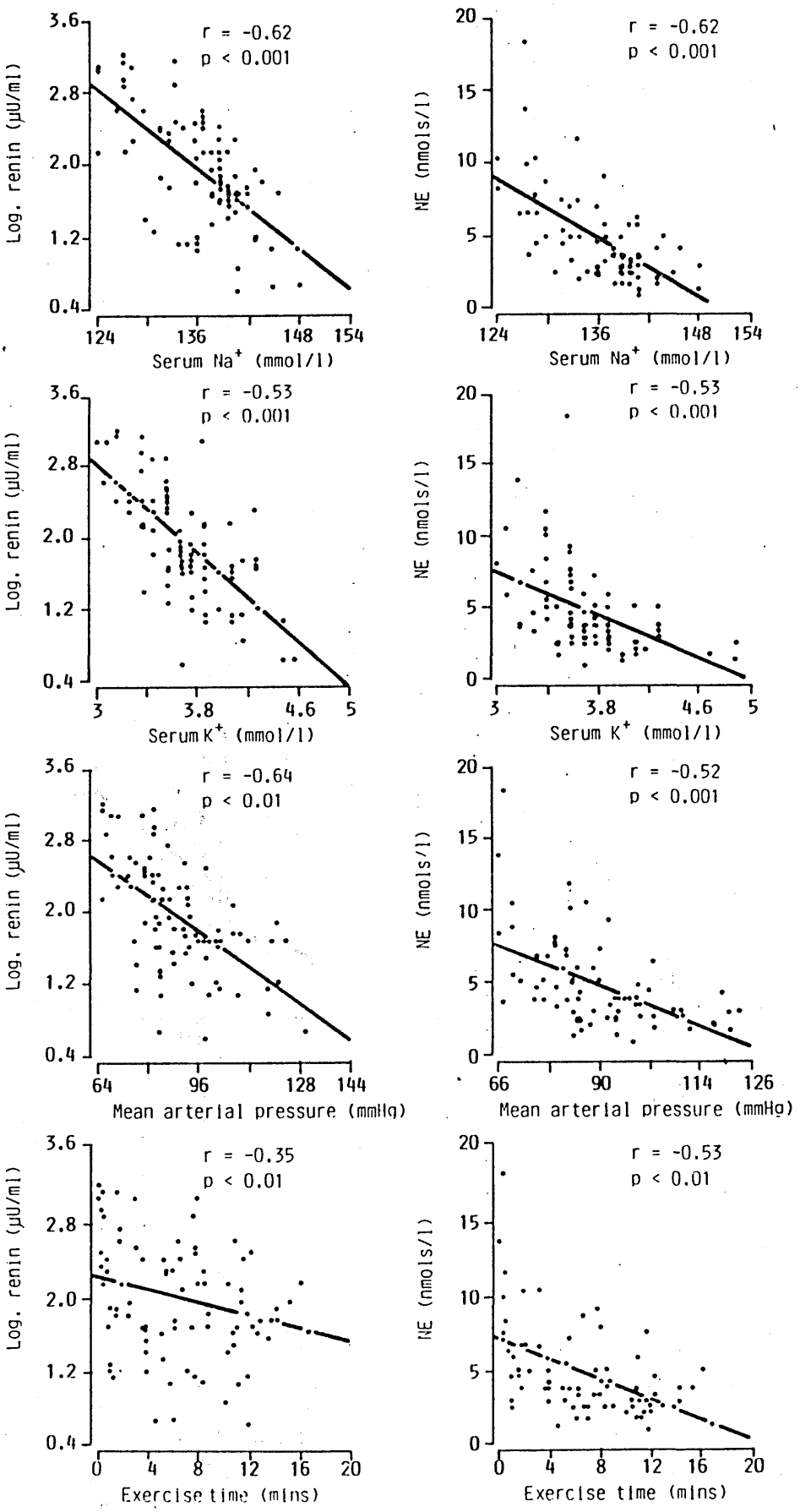


Figure 10.11 Correlation plots showing relationship between circulating neurohormones (plasma active renin concentration (left) and plasma norepinephrine (NE, right) and serum sodium (Na^+) concentration, serum potassium (K^+), mean arterial pressure, and exercise time in patients with congestive heart failure.

assessed by New York Heart Association functional classification) and the plasma active renin concentration accounted for 58% of the observed variation in plasma noradrenaline. If plasma active renin concentration was excluded, then mean arterial pressure was the best predictor, accounting for 46% of the observed variation in plasma noradrenaline.

In addition to the relationships noted above, serum sodium concentration and serum potassium concentration varied linearly and directly with values for mean arterial pressure (r=0.65 and 0.45, respectively). Serum and total body potassium were directly and linearly related (r=0.52), but total body sodium was unrelated to any other variable. **(Figure 10.12)** Forty-three percent of the variability in total body potassium was predicted by the log of plasma active renin concentration. **(Figure 10.13)** Total body potassium depletion was associated with a greater frequency of ventricular ectopics.**(Figure 10.14)**

EFFECTS OF THERAPY IN DESIGNATED SUBGROUPS

During long-term follow-up, patients treated with amiodarone fared better than those who were not ($p<.01$),**(Figure 10.5)** but neither treatment with converting-enzyme inhibitors nor digoxin was related to survival. **(Figure 10.14)**These effects persisted after correction for any differences in prognostic variables between the therapeutic subgroups.

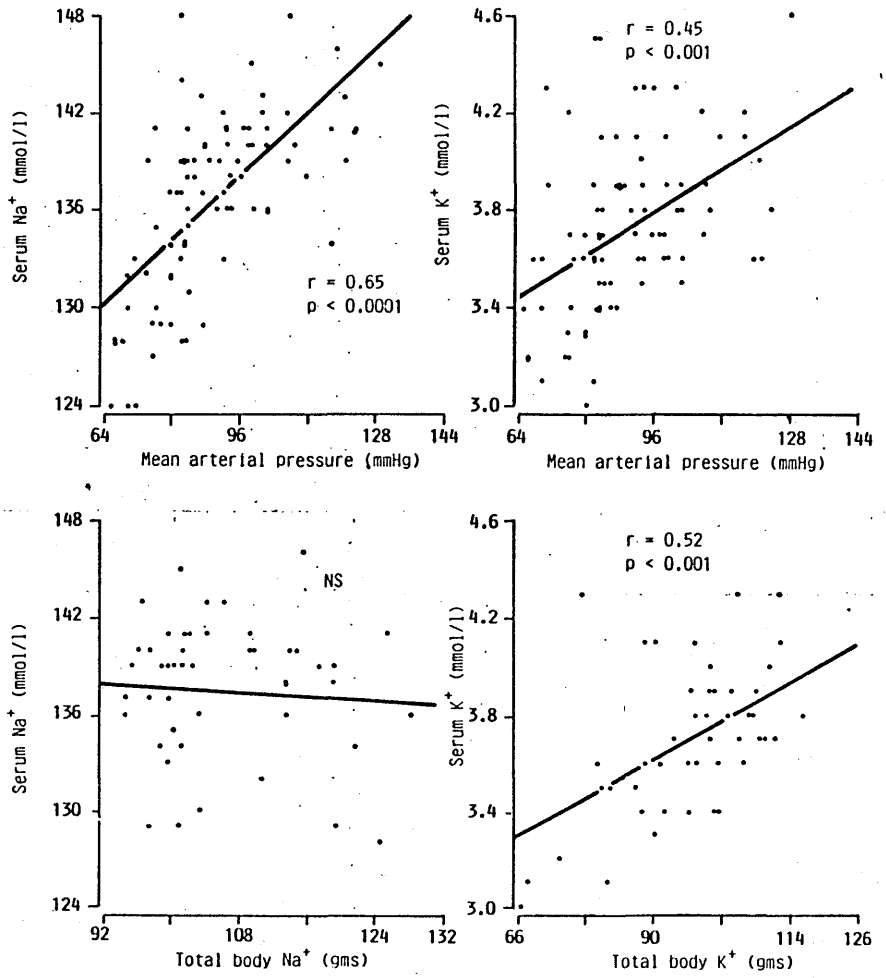


Figure 10.12 Correlation plots showing relationship between serum electrolytes (serum sodium (Na^+) concentration, left) and serum potassium (K^+) concentration, right, and mean arterial pressure and total body sodium in patients with congestive heart failure.

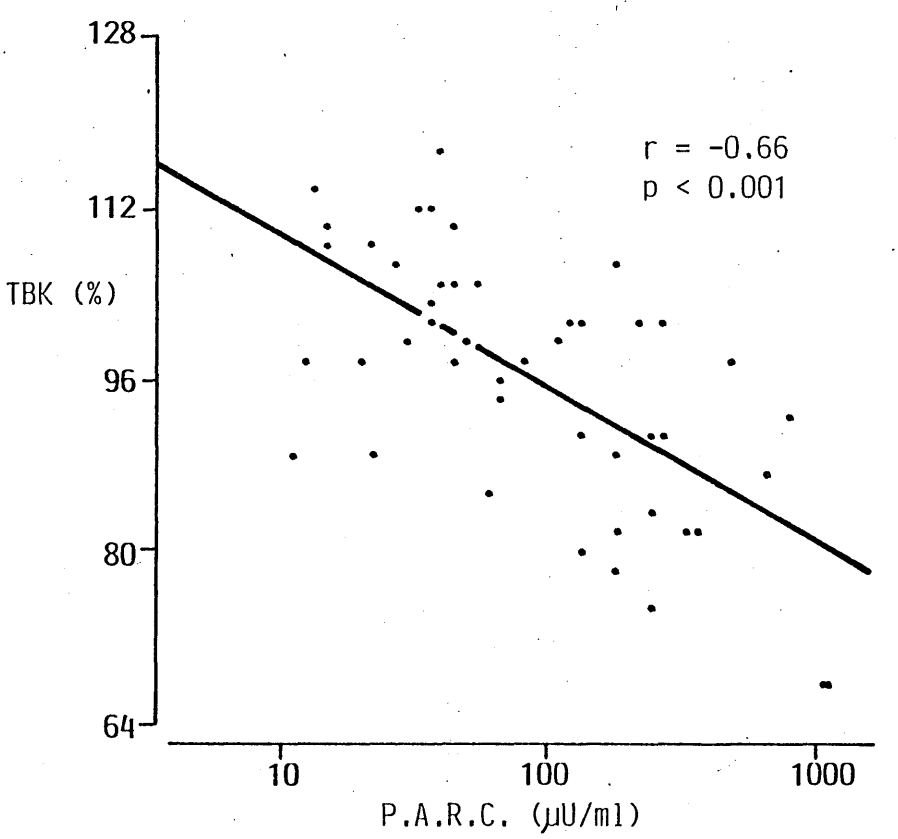


Figure 10.13

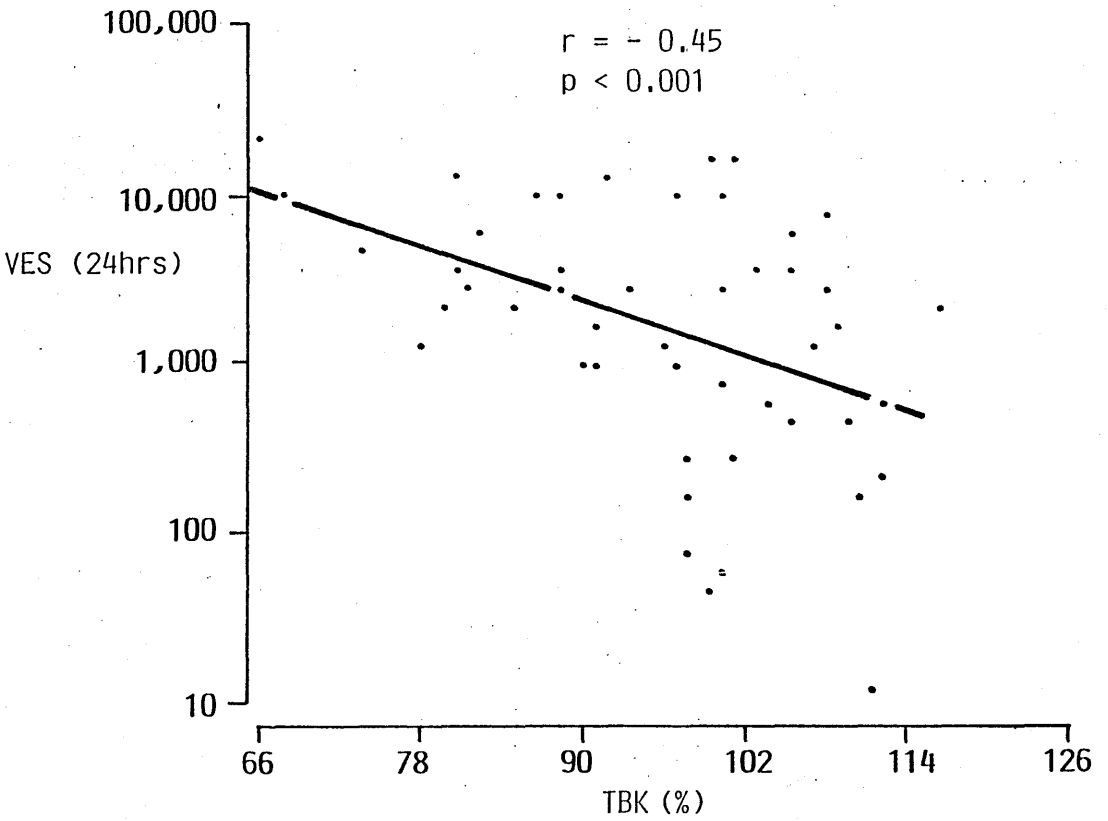
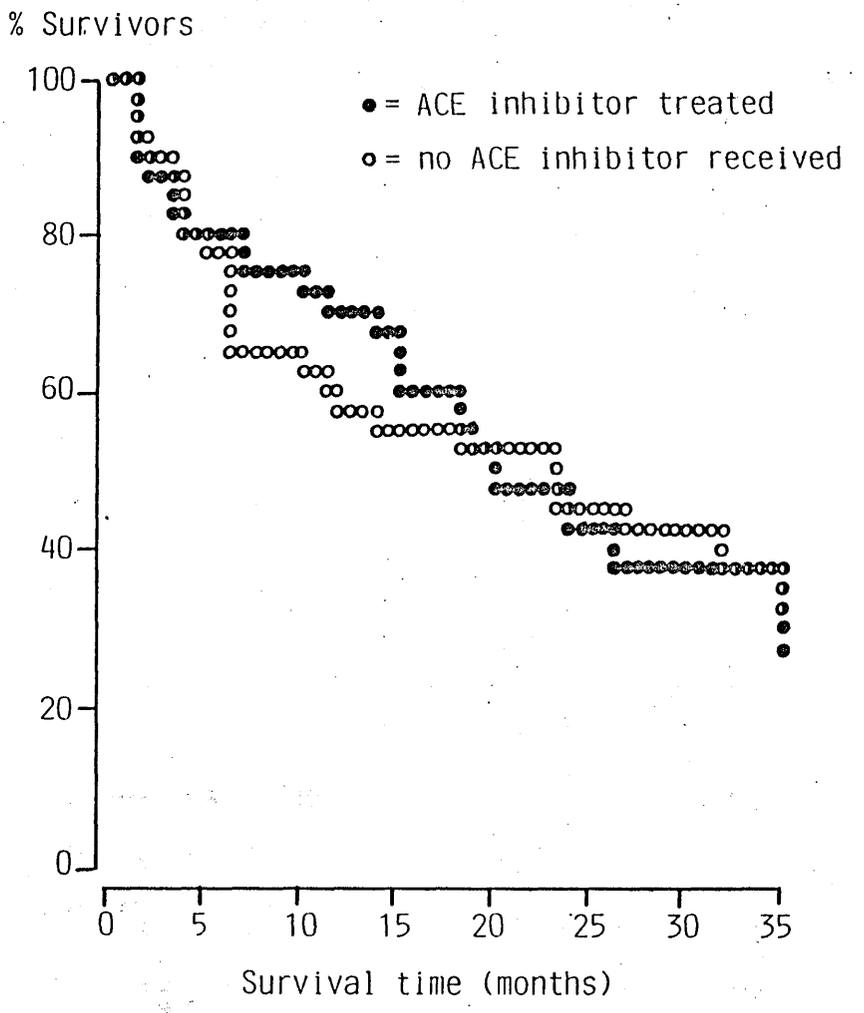

r = - 0.45
p < 0.001
100,000
10,000
1,000
100
10
VES (24hrs)
66
78
90
102
114
126
TBK (%)

Figure 10.14

Figure 10.15 Cumulative Proportion Surviving



CHAPTER 11:HAEMODYNAMICS, ANGIOTENSIN II LEVELS AND SYMPATHOADRENAL FUNCTION AFTER LOW-DOSE CAPTOPRIL IN PATIENTS WITH HEART FAILURE

INTRODUCTION

This study was undertaken to assess the haemodynamic efficacy, likely mode of action, and safety of giving captopril to patients with severe heart failure.

Though several studies have monitored the haemodynamic effects of captopril, many are flawed in their study design (ie comparing basal haemodynamic effects with peak "apparent" effect, instead of some preselected time point), and little attention was paid to the sequence of events at the onset of the drug's action. Most studies agree that the effects of captopril on the venous side of the circulation are equal to or greater than its effects on the systemic side. Therein lies a paradox. Angiotensin II appears to be a predominant arteriolar constrictor with little effect on the venous circulation. If reduction in angiotensin II is indeed the mode of action of angiotensin converting enzyme inhibitors, why the pronounced venous effects? Several investigators have shown that angiotensin II can have effects on the sympathetic nervous system. Perhaps a reduction in sympathetic activity could account for the venodilatation? By giving a low dose of captopril (6.25 mg) and by close haemodynamic and biochemical monitoring it was hoped to throw more light on the mechanisms by which

captopril acted on the circulation. Several authors have noted severe initial adverse responses to these agents, including profound hypotension, renal failure, and death.[691-693] It was therefore felt necessary to study a small population in detail to assess if this was an appropriate initial dose of captopril and how closely the initiation of therapy required to be monitored.

PATIENTS AND METHODS

Ten patients with New York Heart Association functional class III or IV heart failure were studied; the clinical details are shown in Table 11.1. All had symptoms for more than 6 months and were receiving digoxin (mean daily dose 0.2 mg) and frusemide (mean daily dose 196 mg). Vasodilator drugs were discontinued at least one week before the study. The aetiology was idiopathic congestive (dilated) cardiomyopathy in 5 patients, ischaemic heart disease in two patients, and alcoholic cardiomyopathy, chronic aortic regurgitation and chronic mitral regurgitation in one patient each. Eight patients were in sinus rhythm, and two had ventricular rhythm with a controlled ventricular response.

STUDY DESIGN

Patients were studied supine six hours after the last medication and six hours after food. Pulmonary and systemic pressures and cardiac output were measured invasively. Fifteen minutes after final placement of catheters, two

TABLE I Clinical Characteristics

Patient Number	Sex/Age	Medication (mg/day)	Diagnosis	NYHA Grade
1	M/61	Furosemide (240), Digoxin (0.25)	Congestive cardiomyopathy	III
2	M/56	Furosemide (160), Digoxin (0.25)	Congestive cardiomyopathy	IV
3	M/64	Furosemide (120), Digoxin (0.25)	Mitral regurgitation	IV
4	M/54	Furosemide (120), Digoxin (0.25)	Ischemic heart disease	III
5	F/68	Furosemide (120), Digoxin (0.125)	Aortic regurgitation	IV
6	F/70	Furosemide (120), Digoxin (0.125)	Congestive cardiomyopathy	IV
7	M/56	Furosemide (320), Digoxin (0.25)	Ischemic heart disease	III
8	M/64	Furosemide (240), Digoxin (0.125)	Congestive cardiomyopathy	IV
9	F/61	Furosemide (120), Digoxin (0.125)	Congestive cardiomyopathy	IV
10	M/54	Furosemide (200), Digoxin (0.25)	Congestive cardiomyopathy	III

TABLE 11.1

TABLE 11.2

TABLE II Hemodynamic Data

Patient Number	Mean Arterial Pressure (mm Hg)	Pulmonary Artery Diastolic Pressure (mm Hg)	Heart Rate (beats/minute)	Cardiac Index (liters/minute/m^2)	Systolic Vascular Resistance (dynes·second·cm^{-5})	Serum Sodium (mmol/liter)	Renin (μU/ml)	Angiotensin II (pmol/liter)	Norepinephrine (nmol/liter)	Epinephrine (nmol/liter)
1	110	28	69	2.0	3,133	142	4	8	2.7	0.6
2	78	30	108	1.5	3,339	128	2,687	252	20.7	2.8
3	85	40	88	—	—	141	41	25	4.0	<0.1
4	100	25	76	2.2	2,961	139	253	28	2.2	—
5	60	16	76	2.0	3,310	132	1,258	74	—	—
6	80	28	100	1.9	3,692	134	187	22	4.1	0.5
7	88	30	96	2.1	3,343	131	145	9	8.2	1.5
8	72	38	104	2.0	2,529	127	1,329	121	3.6	<0.1
9	80	35	96	2.5	2,581	133	363	35	7.1	0.7
10	75	26	102	2.2	1,873	140	167	32	3.6	0.3

sets of haemodynamic measurements were made, fifteen minutes apart; these varied by less than 5%. Measurements of systolic, diastolic, mean arterial and pulmonary arterial diastolic pressures were then made every 2.5 minutes over a period of 60 minutes, after the patients had been given 6.25 mg captopril by mouth. Cardiac output was measured at baseline, 30 minutes and 60 minutes. The plasma concentrations of active renin, angiotensin II, noradrenaline and adrenaline were measured in arterial blood samples taken every 5 minutes. Serum sodium was also measured prior to giving captopril.

STATISTICAL METHODS

Results are expressed as mean $\pm$ standard deviation. Correlations were calculated by the method of least squares. For pressures, heart rate and hormonal measurements, correlations were calculated for each variable with time. Statistical significance was derived from a two-way sign test on the slopes of the correlations. Paired t-tests with Bonferroni's correction were used to analyse changes in cardiac index and systemic vascular resistance. The same method was used to assess changes in plasma concentrations of angiotensin II, since an increase in plasma levels towards the end of the study period compromised the correlation with time. Values of $p<0.05$ were considered significant.

RESULTS

Haemodynamic Effects

Measurements of haemodynamic variables before and after treatment are given in Table 11.2. Decreases in systolic and diastolic pressures in the radial and pulmonary arteries together with a reduction in heart rate were evident 20 - 30 minutes after captopril, with maximal effects between 45 and 50 minutes after drug intake. **(Figure 11.1)** Some recovery was noted by 60 minutes after dosing.

The percentage decreases in left ventricular filling pressure were similar to and well correlated with the decreases in systemic arterial pressure; both these variables also correlated with the decrease in heart rate (r values for correlations between 0.73 and 0.91; $p<0.01$). Cardiac index increased slightly from 2.0 $\pm$0.3 to 2.3 $\pm$ 0.4 litres/minute/m2, 30 minutes after captopril, and 2.3 $\pm$ 0.1 litres/minute/m2, 60 minutes after the drug ($p<0.05$}. Systemic vascular resistance fell markedly from 2973$\pm$558 to 2357$\pm$699 dynes.second.cm- 2, after 30 minutes and 1500 + 470 dynes.second.cm-5, after 60 minutes ($p<0.01$).

Three patients (patients 3, 4 and 5) showed evidence of vasomotor syncope in the supine position, with a feeling of faintness and warmth associated with bradycardia, pallor, and sweating. Mean blood pressure fell by an average of 46% in this group, compared with 17% in the other patients. Pulmonary artery diastolic pressure also fell markedly (51%

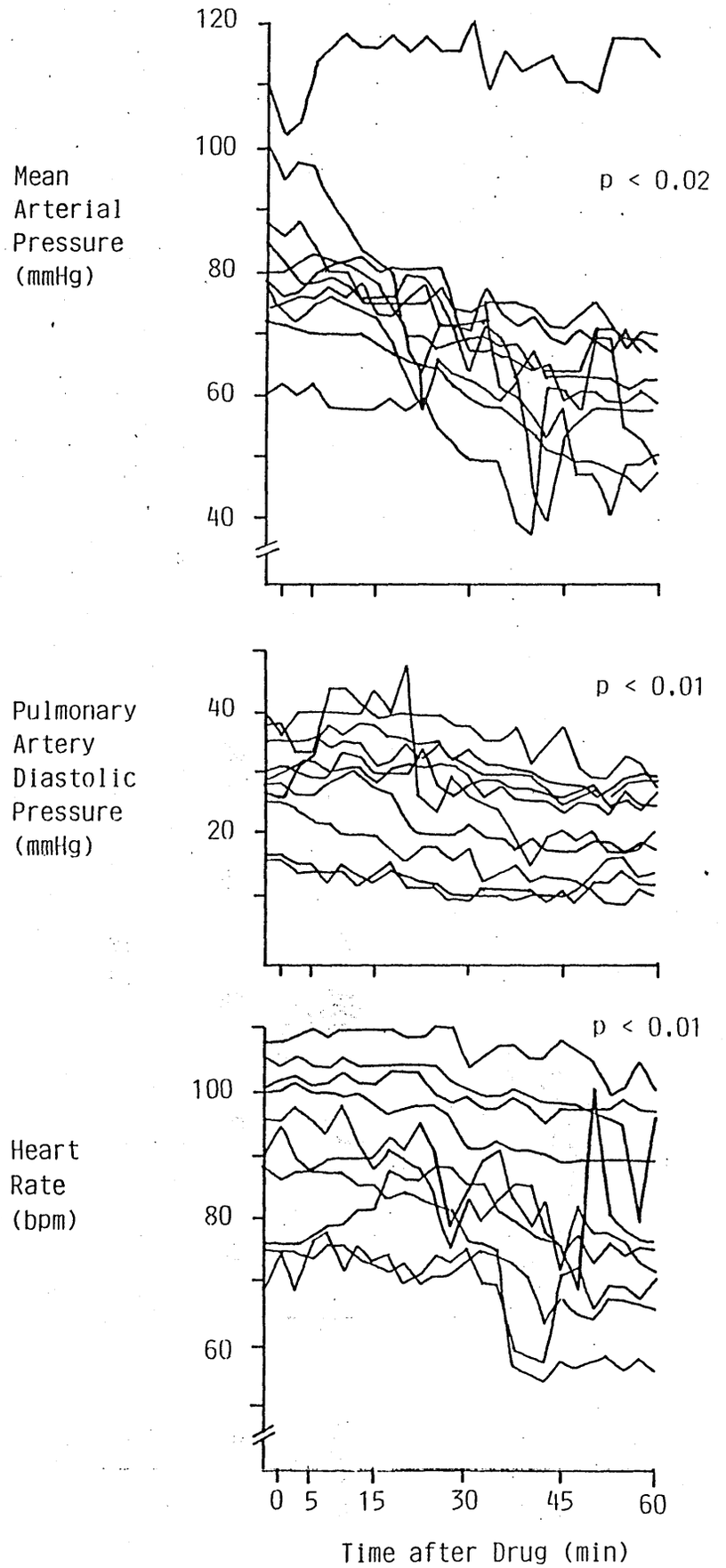


Figure 11.1 Individual responses of mean arterial pressure, pulmonary artery diastolic pressure, and heart rate to captopril. The sudden increase in heart rate between 45-60 minutes in one patient after drug intake followed intravenous injection of atropine.

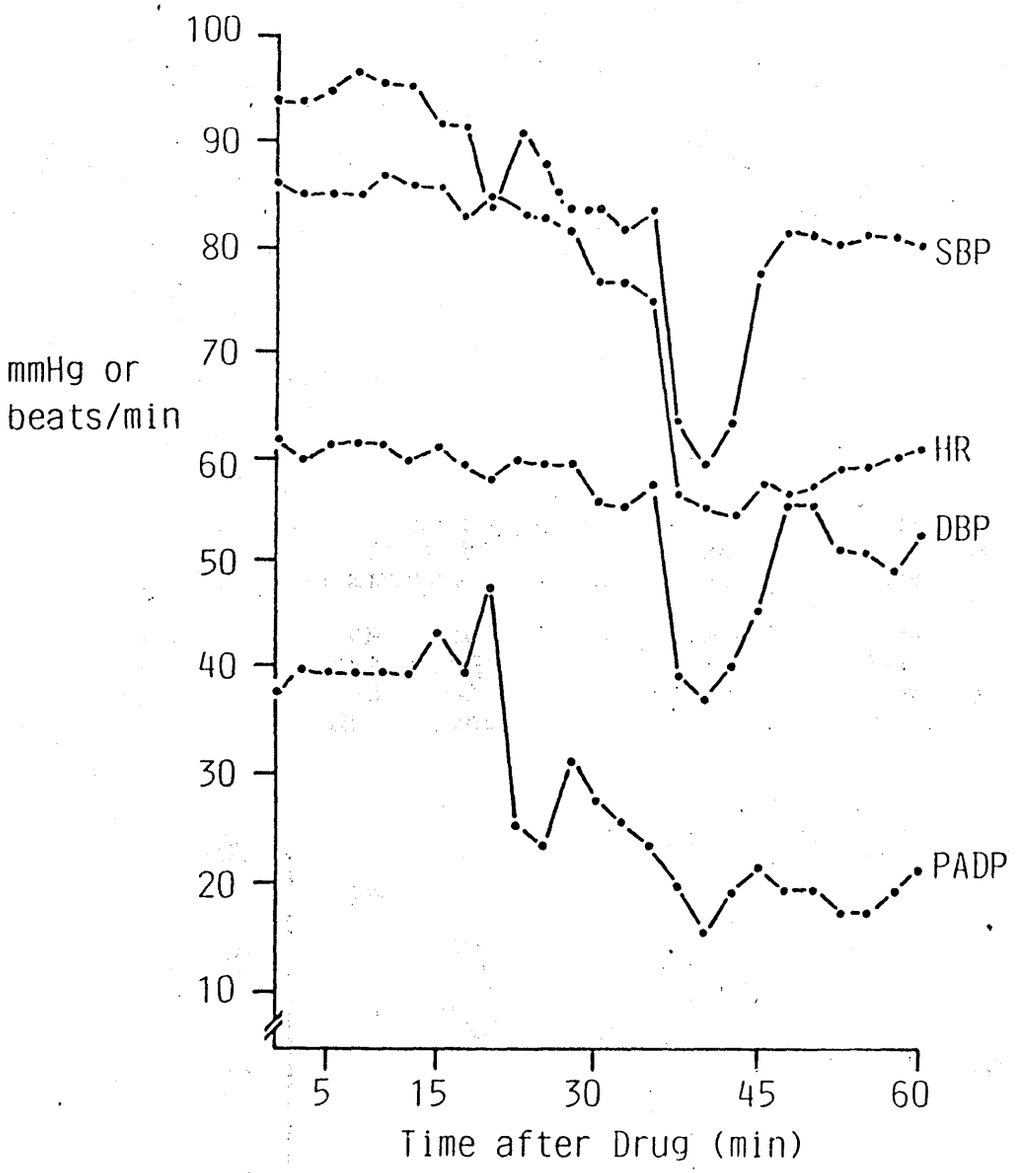
compared with 23%), as did the heart rate (23% compared with 9%). The haemodynamic results from a patient who showed evidence of vasomotor syncope is depicted in Figure 11.2. Note the decline in pulmonary artery diastolic pressure before the abrupt onset of bradycardia and systemic hypotension. The overall timing of the fall in systemic arterial pressure was no different from the timing of the decline in pulmonary arterial diastolic pressures, with detectable falls occurring at 20 minutes. In contrast, in those patients who developed vasomotor syncope, a marked decline in left ventricular filling pressures, as reflected by pulmonary arterial diastolic pressure, preceded haemodynamic collapse.

Angiotensin II, Renin and Catecholamines

Plasma active renin concentration before captopril was high in 9 patients and suppressed in one, a patient with marked peripheral oedema. There was significant inverse correlation between the serum sodium and renin ($r=-0.72; p<0.01$). Although plasma concentrations of renin tended to be highest in those patients with the lowest cardiac output, the percentage decrease in systemic vascular resistance and increase in cardiac output after captopril were not well correlated with plasma concentrations of angiotensin II or renin before treatment ($r=0.1-0.2$). There was a closer relationship between the initial serum sodium concentration and the percentage change in systemic vascular resistance after captopril

Figure 11.2 This represents the haemodynamic response to captopril in Patient 3, in whom vasomotor syncope developed 40 minutes after captopril administration.

SBP = radial artery systolic pressure
DBP = radial artery diastolic pressure
PADP= pulmonary artery diastolic pressure
HR = heart rate



(r=0.5), but this was not statistically significant. Plasma concentrations of renin increased after captopril in 9 patients but failed to increase in the patient with initially low levels. This patient had the highest initial arterial pressure, and was later observed to have suppressed levels of aldosterone also (patient 1). Plasma concentrations of angiotensin II fell progressively to reach a nadir about 40 minutes after drug intake **(Figure 11.3)**, a time that coincided with the greatest haemodynamic change. A sensitive index of angiotensin converting enzyme inhibition is the ratio of plasma concentrations of renin to angiotensin II. From this index, it is clear that the drug had an effect 15 minutes after administration **(Figure 11.4)** and that this coincided with the apparent onset of haemodynamic changes.

Plasma concentrations of noradrenaline also fell, despite the large reductions in arterial pressure. Plasma concentrations of adrenaline varied markedly, in- keeping with the pulsatile nature of adrenaline release. Large increases in plasma adrenaline were noted during syncope but arterial plasma noradrenaline failed to increase. One patient who developed marked bradycardia was given 1.2 mg atropine with a subsequent increase in heart rate and systemic and pulmonary pressures.

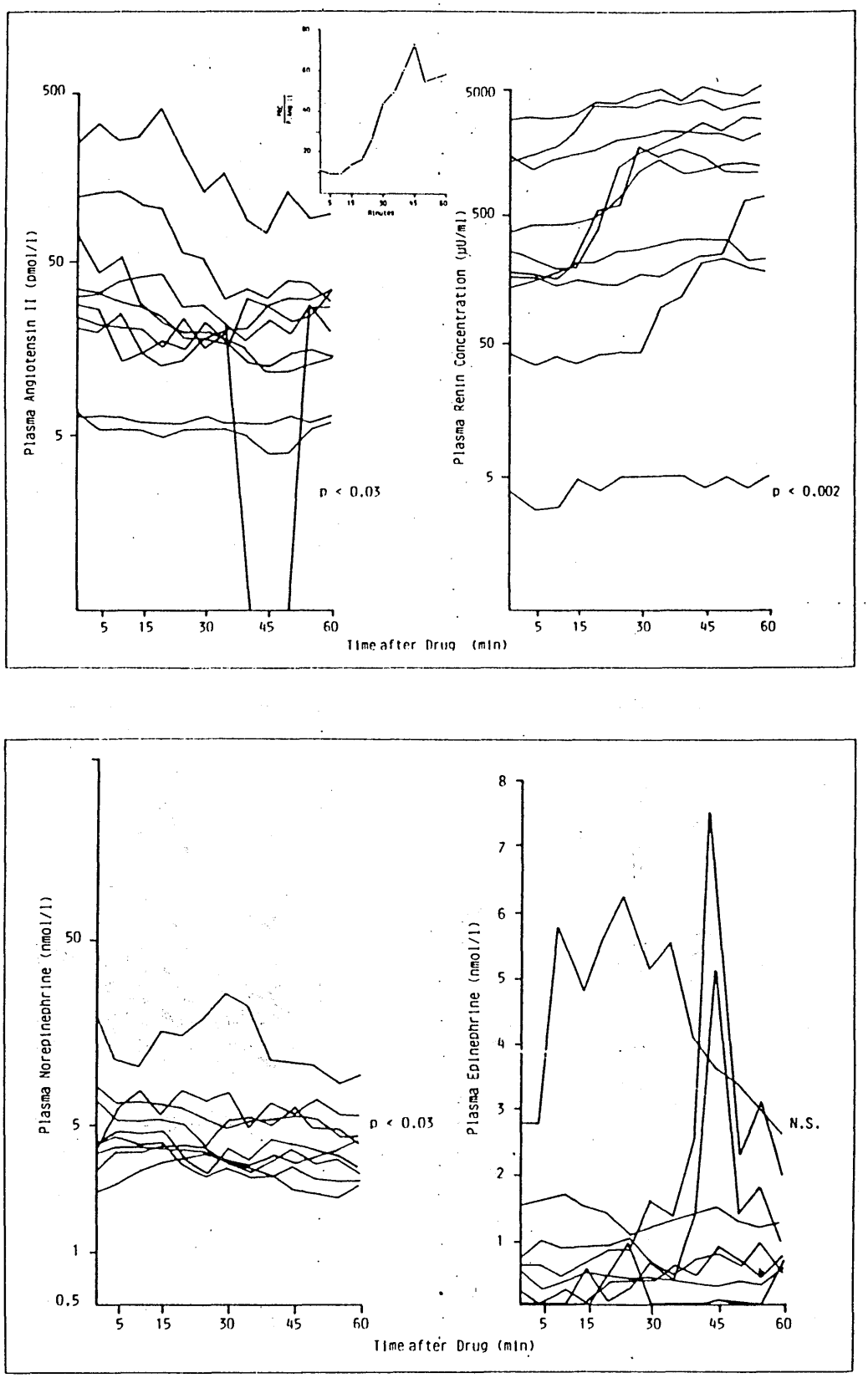


Figure 11.3 This shows the individual responses in plasma concentrations of angiotensin II, renin, (the ratio of renin to plasma angiotensin II is shown in the inset), plasma noradrenaline, and plasma adrenaline.

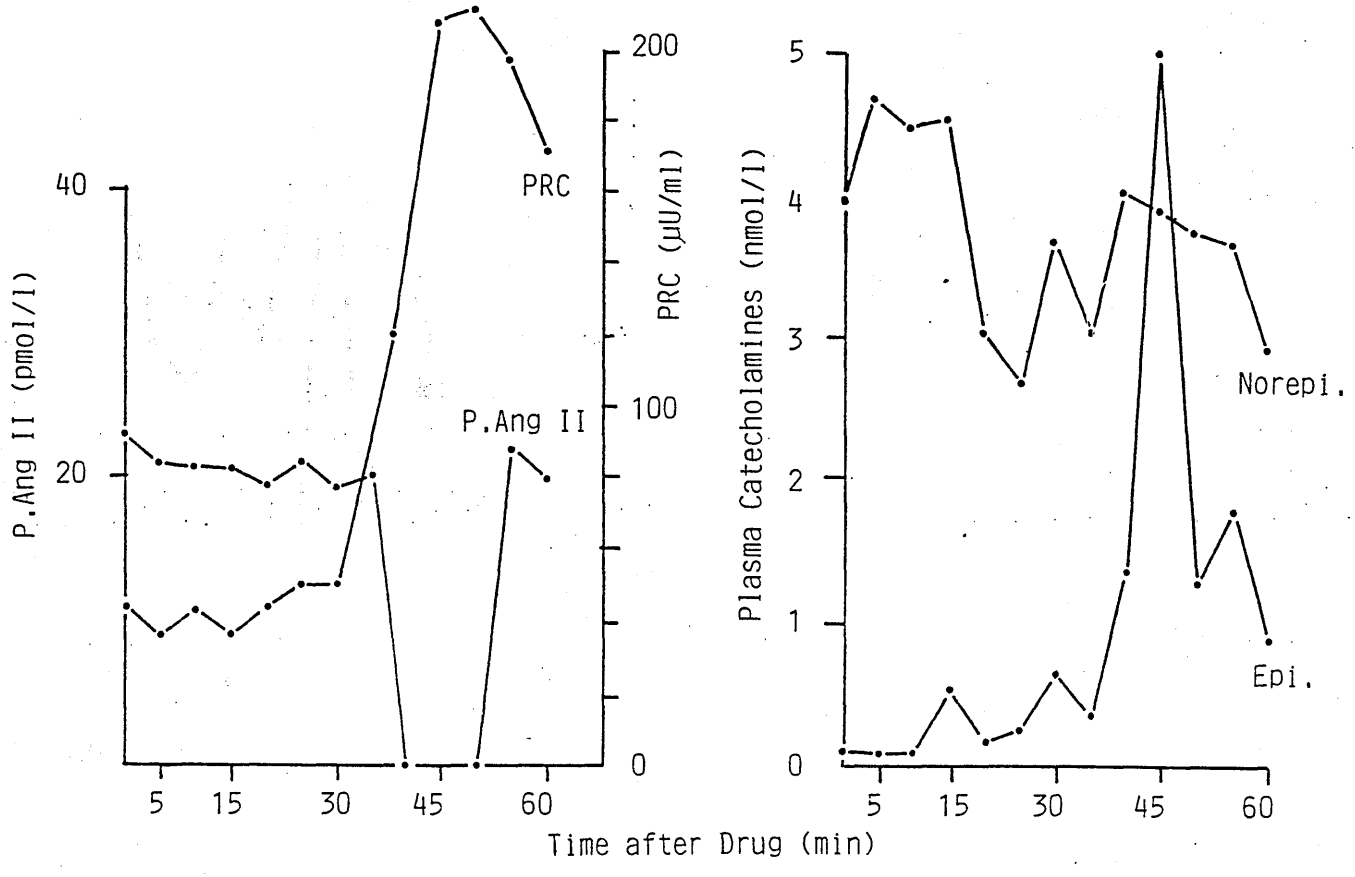


Figure 11.4 Plasma concentrations of renin, angiotensin II, noradrenaline, and adrenaline after captopril in Patient 3, who had a vasomotor syncope.

CHAPTER 12: SEVERE HYPOTENSION AFTER FIRST DOSE OF ENALAPRIL IN HEART FAILURE

INTRODUCTION

Enalapril was the second orally active converting enzyme inhibitor to become available for use in hypertension and heart failure. Occasional severe hypotension has been described after the first dose of captopril in patients with heart failure and hypertension. Syncope with captopril administration coincides with a rapid fall in angiotensin II concentration, which occurs usually within 30-45 minutes after oral dosage. Unlike captopril, enalapril requires conversion by the liver to the active metabolite enalaprilat, this delaying the onset of action.[694,695] We report the effects of enalapril in a consecutive series of 26 patients with cardiac failure, with particular reference to the time of onset of the hypotensive effect and its magnitude.

PATIENTS AND METHODS

Twenty-six patients were studied (mean age 59+4(SD) years) with moderate to severe heart failure (New York Heart Association Class II-IV; median III) of more than 6 months' duration and for which treatment with diuretics and digoxin had remained unchanged for at least a month. All patients received frusemide in a mean dose of 123 (SD 60) mg/day and, in addition, 4 were taking bendrofluazide 5-10 mg/day, and 7 amiloride 5-10 mg/day. All were also receiving

digoxin (0.22 (SD 0.05) mg/day). All patients had a dilated, poorly functioning left ventricle on echocardiography. The aetiology of heart failure was ischaemic heart disease in 14, idiopathic dilated cardiomyopathy in 10, and severe residual impairment of left ventricular function after valve replacement in 2. No patient was noticeably hypertensive before treatment and all had systolic pressures above 90 mm Hg.

Before being given enalapril, the serum urea, creatinine and electrolytes, and plasma active renin (normal range 10-50 mU/l) angiotensin II (normal range 5-35 pmol/l;53-368 pg/100 ml) concentrations were measured. Plasma catecholamines and vasopressin values were also assayed in one patient. Diuretics were administered with the enalapril in the first 20 patients but withheld for 24 hours in a further 5, including cases 1 and 2. Blood pressure was recorded routinely before and 4 hours after the first dose of enalapril. Further readings were taken if the patient noted any symptoms. Mean blood pressure was calculated as (systolic - diastolic)/3 (+ diastolic). Patients were kept in bed for a minimum of 4 hours after the first dose of enalapril. Angiotensin II (Hypertensin; Ciba) was given by intravenous infusion when required.

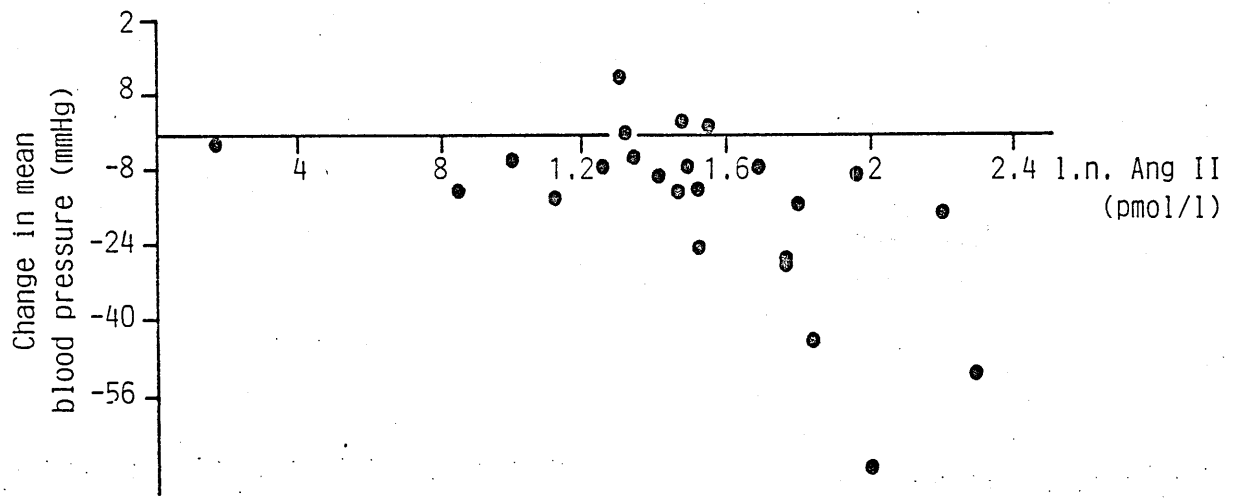


Figure 12.1 Relation between log plasma angiotensin II and fall in mean blood pressure (Spearman's rank correlation $r=-0.59;p<0.01$)

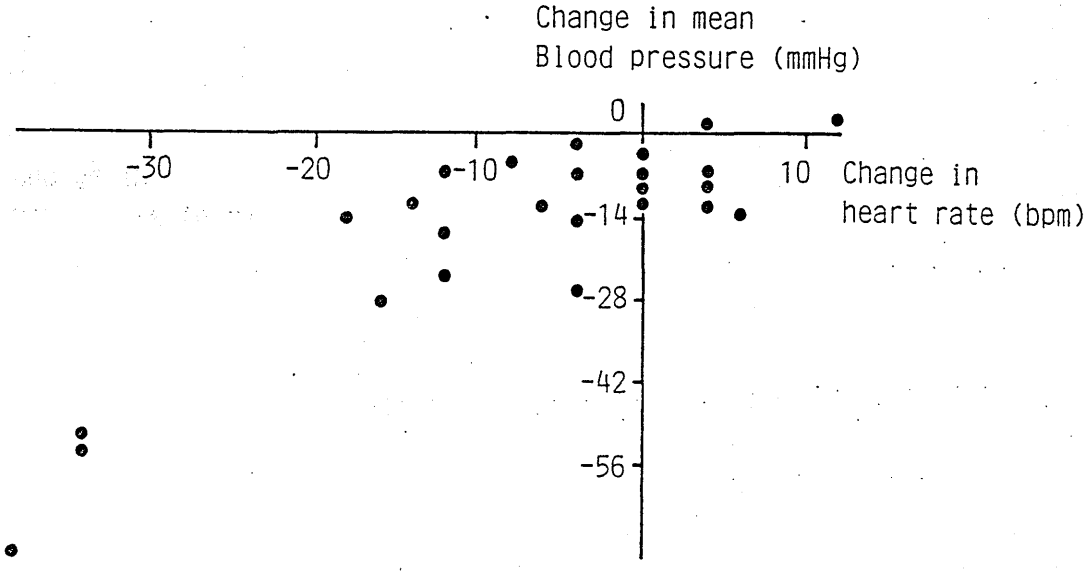


Figure 12.2 Relation between fall in mean blood pressure and fall in heart rate (Spearman's rank correlation $r=-0.66;p<0.002$)

STATISTICS

Correlations were performed using the least squares technique for normally distributed data and Spearman's rank correlations for non-parametric data. The response to treatment was tested by Student's t test with prior log transformation of the data where indicated. A p value of <0.05 was considered significant.

RESULTS

Before enalapril, plasma sodium and plasma active renin concentrations were closely and inversely correlated ($r=-0.75;p<0.001$). The change in blood pressure with the first dose of enalapril was modestly correlated with the pre-treatment plasma active renin ($r=-0.42;p<0.05$) and angiotensin II ($r=-0.59;p<0.01$) concentrations (Figure 12.1) but the correlation with serum sodium was not significant ($r=0.34;NS$).

In the first 20 patients, enalapril caused no adverse effects. Subsequently, after the first dose, 3 patients developed profound hypotension, bradycardia (Figure 12.2) and sweating. The falls in heart rate and mean blood pressure were significantly correlated ($r=0.66;p<0.002$). Table 12.1 shows the treatment and baseline recordings of 3 patients who developed severe hypotension (cases 1-3) compared with the mean (and median where appropriate) values of the 23 patients who did not.

The occurrence of syncope could not predicted by initial mean blood pressure **(Figure 12.3)**, initial serum sodium **(Figure 12.4)**, frusemide dose **(Figure 12.5)**, or the creatinine/urea ratio (an index of prerenal uraemia). **(Figure 12.6)**

CASE HISTORIES OF PATIENTS WITH SYNCOPE

Case 1:

A 64-year-old man with a history of 2 myocardial infarctions was admitted with orthopnoea. His jugular venous pressure was raised and he had an enlarged liver and peripheral oedema. Diuretics were withheld for 24 hours and 10 mg enalapril administered. Four hours later he abruptly developed syncope (Table 12.1). Head- down tilt and infusion of angiotensin II (6 ng/kg/minute) restored his blood pressure to 92/64 mm Hg but bradycardia persisted. Attempts to withdraw angiotensin resulted in further syncopal episodes until 24 hours afterwards, when it was stopped, the blood pressure remaining at 90/66 mm Hg and the heart rate at 62 beats/minute. Four hours after the onset of syncope a 12-lead electrocardiogram showed new anterior T wave inversion. The myocardial specific creatinine kinase MB fraction was mildly raised 18 hours later (239 IU, 8% of total creatinine kinase; normal range <160 IU, <6%). In the 24 hours after stopping the infusion of angiotensin II he passed 2.7 litres of urine (sodium 72 mmol(mEq)/l, creatinine 2.4 mmol/l(27.1 mg/100ml). Serum

TABLE 12.1

TABLE I—*Comparison of patients with and without hypotension on first administration of enalapril*

	Case 1	Case 2	Case 3	Group mean (SD) [range]	p Value*
Age (years)	64	61	66	58 (4) [48-65]	
New York Heart Association functional class	IV	III	III	III [II-IV]	
Systolic blood pressure (mm Hg):					
Basal	106	120	128	120 (22) [92-166]	p<0·001
Nadir	40	56	38	108 (25) [72-154]	
Mean blood pressure (mm Hg):					
Basal	78	93	97	89 (12) [72-121]	p<0·001
Nadir	27	39	26	79 (15) [60-109]	
Heart rate (beats/min):					
Basal	78	86	82	81 (11) [64-102]	p<0·05)
Nadir	44	52	34	77 (10) [58-94]	
Basal plasma active renin concentration (mU/l)	695	191	202	132 [3-828]; median = 61	
Plasma angiotensin II (pmol/l):					
Basal	196	64	58	57 [0·5-229]; median = 30	p<0·01
Four hours	ND	16	18	26 [0·5-72]; median = 23	
Serum sodium (mmol/l)	136	139	132	138 (4) [129-143]	
Serum urea (mmol/l)	8·5	8·0	15·6	6·7 (2·4) [3·8-12·6]	
Serum creatinine (μmol/l)	134	119	228	102 (25) [68-162]	
Dose of enalapril (mg)	10	5	5	5	
Dose of frusemide (mg/day)	160	120	200	118 (61) [60-240]	
Dose of bendrofluazide (mg/day)	5	—	10	See text	

ND = Not done.
* Significance of response to enalapril.
Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 10·5 pg/100 ml. Sodium: 1 mmol/l = 1 mEq/l. Urea: 1 mmol/l ≈ 6 mg/100 ml. Creatinine: 1 μmol/l ≈ 11·3 μg/100 ml.

TABLE 12·2

TABLE II—*Plasma hormone concentrations in case 2 before and after enalapril*

	Active renin (mU/l)	Angiotensin II (pmol/l)	Noradrenaline (nmol/l)	Adrenaline (nmol/l)	Vasopressin (ng/l)
Basal	191	64	4·1	0·1	0·3
2·5 hours	2096	16	3·8	0·4	1·6

Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 10·5 pg/100 ml. Noradrenaline: 1 nmol/l ≈ 169 pg/ml. Adrenaline: 1 nmol/l ≈ 183 pg/ml.

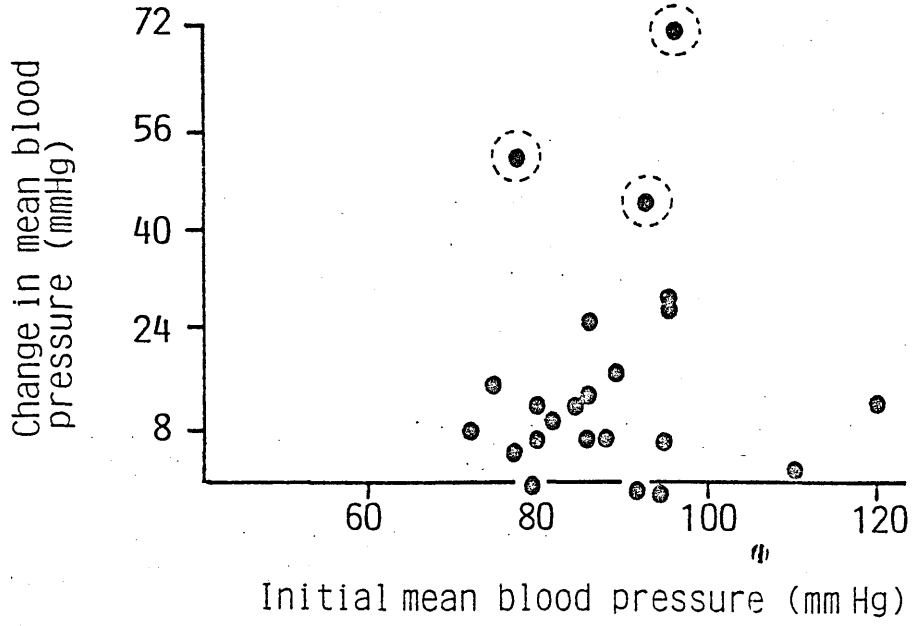


Figure 12.3 Relationship between initial mean blood pressure and change in mean blood pressure. Patients who developed syncope have circled values.

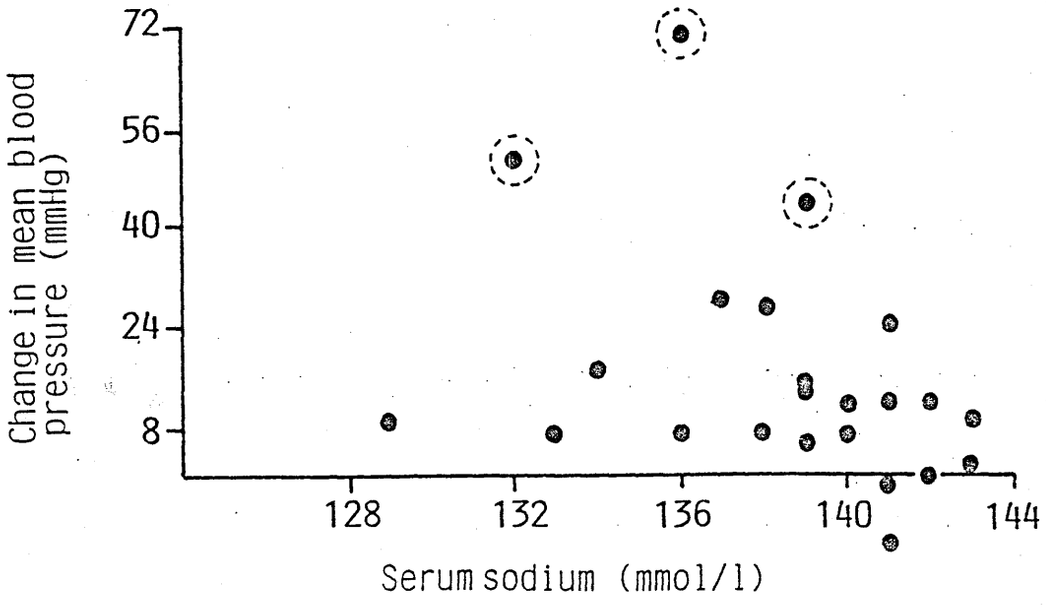


Figure 12.4 Relation between serum sodium and change in mean blood pressure. Patients who developed syncope have circled values.

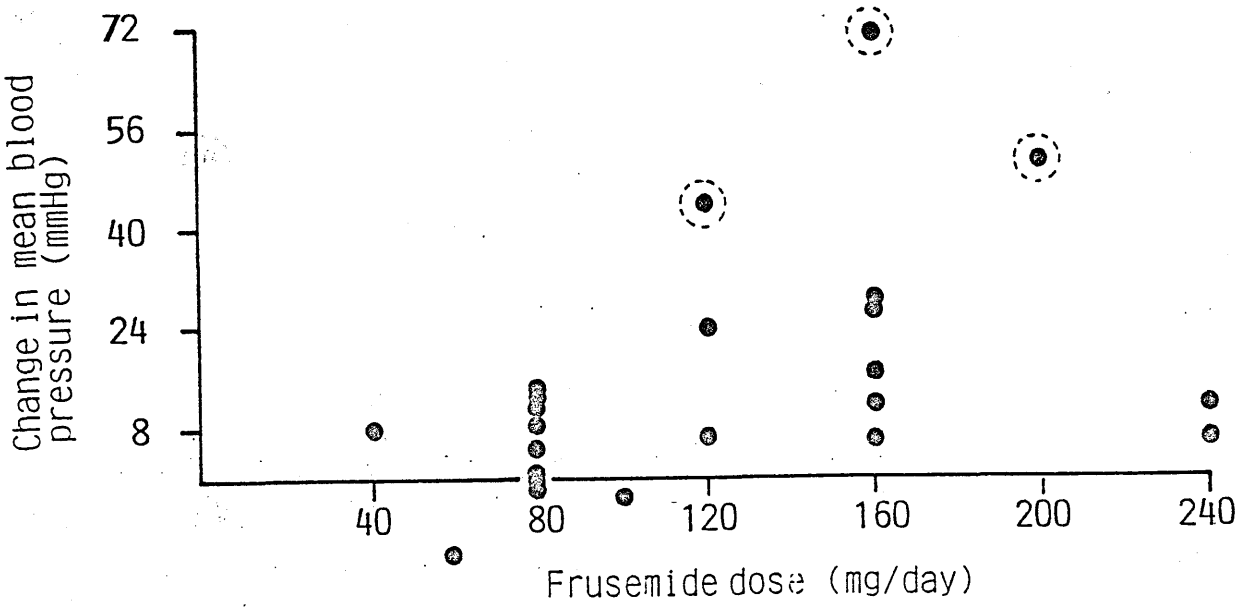


Figure 12.5 Relation between frusemide dose and change in mean blood pressure. Patients who developed syncope have circled values.

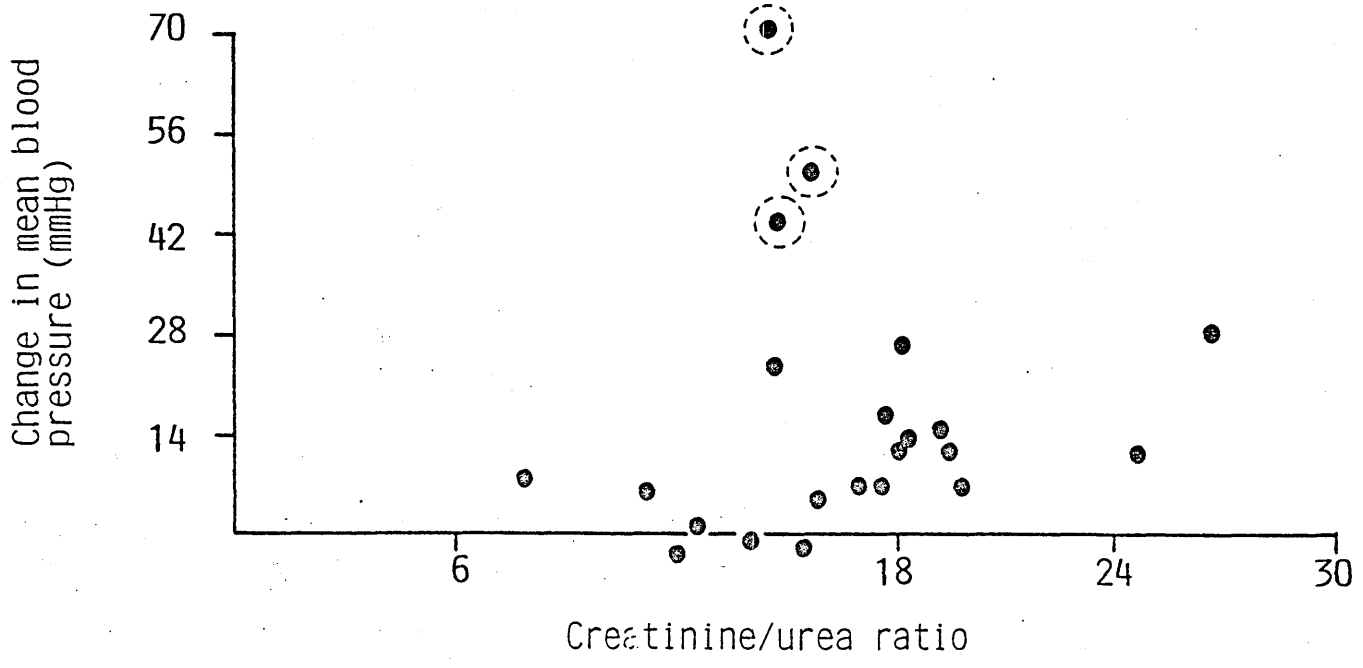


Figure 12.6 Relationship between creatinine/urea ratio and change in mean blood pressure. Patients who developed syncope have circled values.

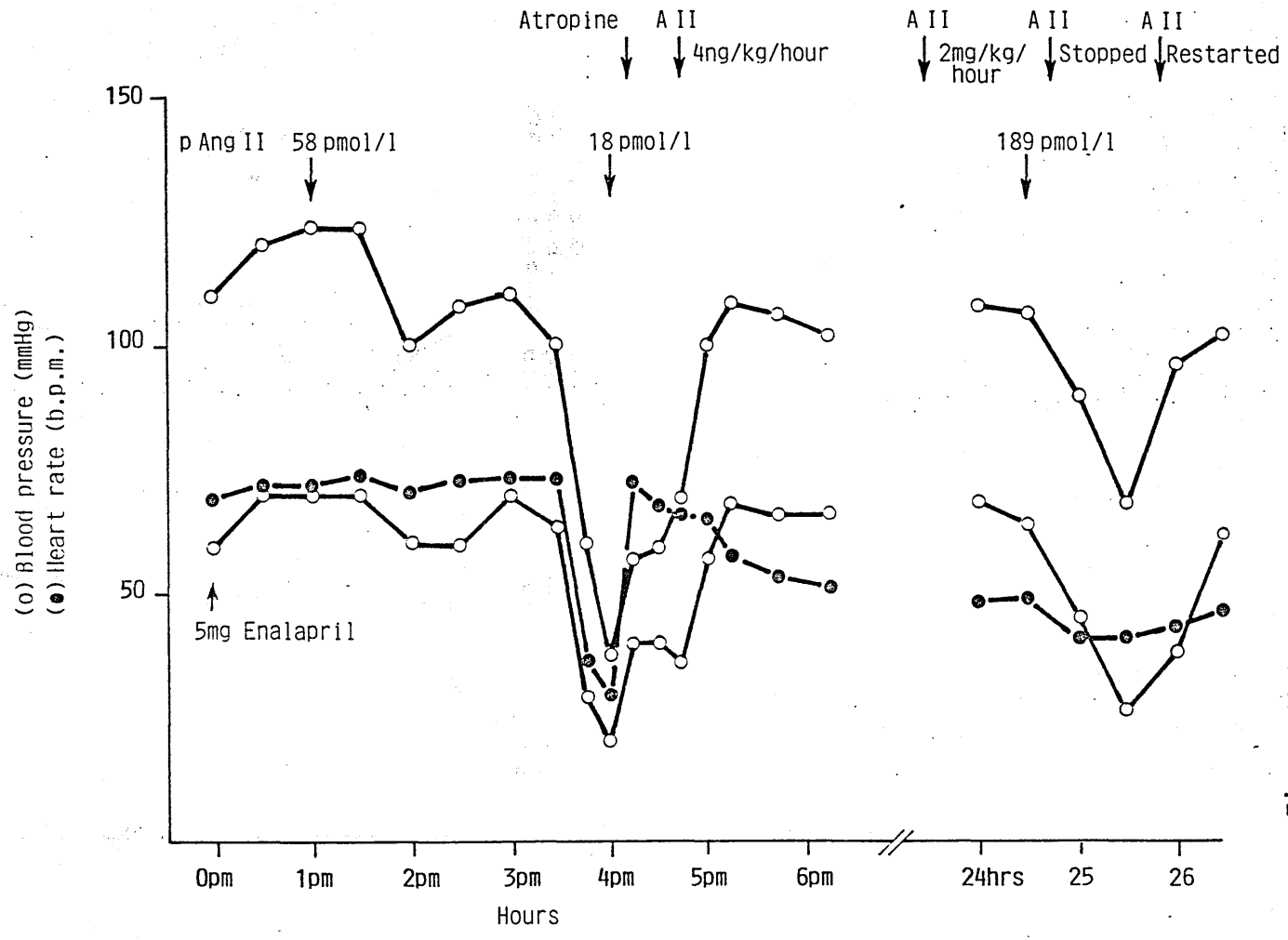


Figure 12.7 Case 3. Changes in systolic (closed circles) and diastolic (open circles) blood pressure and heart rate (triangles) after 5 mg enalapril by mouth.

sodium fell to a nadir of 124 mmol(mEq)/l and creatinine rose to 297 umol/l(1.4 mg/100ml; see Table 12.1 for initial values). Forty-eight hours later the patient received 2.5 mg enalapril without ill effect, his systolic pressure remaining above 80 mm Hg. In the following months, he had a good symptomatic response to the drug, with a reduction in diuretic requirements and improved exercise performance.

Case 2:

A 61-year-old man with a history of 3 myocardial infarctions was admitted with orthopnoea and dyspnoea. The jugular venous pressure was raised. Diuretics were withheld for 24 hours and he was given 5 mg enalapril. Two and a half hours later, however, he felt faint; blood pressure fell from 94/74 to 56/30 mm Hg and heart rate from 82 to 52 beats/minute over 15 minutes. Blood samples showed that the previously high plasma angiotensin II concentration had fallen into the normal range, while the plasma active renin concentration showed a brisk rise (Table 12.2). Plasma noradrenaline concentration failed to rise in response to the fall in blood pressure but adrenaline and anti-diuretic hormone increased. Head-down tilt increased his pressure to 78/42 mm Hg; heart rate remained at 56 beats/minute. After 1.2 mg atropine given 15 minutes later, his blood pressure increased to 90/64 mm Hg and heart rate to 70/minute. After a further 24 hours of bed rest he was given 2.5 mg enalapril, without ill effect. Subsequently, he had a good

symptomatic response, with an increase in exercise performance.

Case 3:

A 66-year-old man with a dilated cardiomyopathy was admitted with increasing dyspnoea. Jugular venous pressure was raised. Diuretics were not withheld. Two and a half hours after a 5 mg dose of enalapril, he became abruptly hypotensive with bradycardia **(Figure 12.7)**. Plasma angiotensin II concentration had fallen from 58 to 18 pmol/l (609-189 pg/100 ml). After 1-2 mg atropine given 10 minutes later, his blood pressure increased from 38/20 to 58/40 mm Hg, and pulse rate from 38 to 50 beats/minute. An angiotensin II infusion (6 ng/kg/minute) partially restored his blood pressure to 90/74 mm Hg, although bradycardia persisted at 54 beats/minute. Attempts to stop the angiotensin II infusion resulted in a further episode of syncope. Diuretics were withheld for the next 4 days. Angiotensin II concentration measured 24 hours after the initial syncopal episode and during an infusion of 2 ng/kg/hour was 189 pmol(1985 pg/100 ml), though blood pressure and heart rate were incompletely restored (108/68 mm Hg;64 beats/minute). Forty-eight hours after the initial syncope, 1 litre physiological saline was infused over 2 hours, and angiotensin II discontinued, without further syncope. Over 48 hours of oliguria, his serum sodium concentration fell to 120 mmol(mEq)/l and serum creatinine value rose to 430 umol/l(4.9 mg/100ml). A diuresis ensued

after stopping angiotensin II (24-hour urine volume 3.7 litres; sodium concentration 105 mmol(mEq)/l, creatinine 1.8 mmol/l(20.4 mg/100ml). Three days later, 2.5 mg enalapril was administered, without untoward effect. Subsequently, he had a fair clinical response in terms of symptoms and exercise performance.

CHAPTER 13: OBSERVATIONS ON THE ORAL DOSE OF CAPTOPRIL REQUIRED FOR HAEMODYNAMIC EFFECT

INTRODUCTION

The previous section demonstrated that 6.25 mg captopril given orally could cause an alarming fall in blood pressure in some patients, and the previous two chapters have shown that this group cannot be reliably identified. This raises the question "Is there a safe therapeutic window in which haemodynamic changes will occur but without syncope in subjects at high risk?"

PATIENTS

Two patients were studied, aged 63 and 58 years. Each had previously been given 6.25 mg captopril, causing marked hypotension and symptoms suggestive of incipient vasomotor syncope. At least one week had been allowed to elapse between this event before the present observations were made. The aetiology of heart failure was ischaemic heart disease in both. One was on frusemide 240 mg/day, the other on frusemide 200 mg/day, plus 5 mg bendrofluazide. Both received digoxin 0.25 mg/day. One had marked left ventricular failure, the other had evidence of both right and left ventricular failure, with the former predominating.

METHODS

Patients were studied on bed rest, and medication was withdrawn for the day of study. A Swan-Ganz catheter was placed in the pulmonary artery for the measurement of pulmonary artery pressures 30 minutes before the study. Blood pressure was monitored by mercury sphygmomanometer every 15 minutes. Captopril was given every 2 hours, according to the following regime: 1 mg, 2 mg, 3 mg, 4 mg, etc, as tolerated. Any symptoms of hypotension or a fall in systolic arterial pressure of greater than 25% was considered a suitable end-point. Angiotensin II infusion was readied in case of need. Blood was taken prior to the study and 40 minutes after dosing or during any episode of marked hypotension for plasma levels of renin, angiotensin II, noradrenaline, adrenaline and anti-diuretic hormone.

RESULTS

No haemodynamic effect could be detected in either patient after 1 mg and 2 mg does of captopril. Both patients dropped their blood pressures markedly after 3 mg captopril. This was accompanied by feelings of faintness and a fall in pulmonary arterial pressures, pulmonary capillary wedge pressure and heart rate. At this time, plasma levels of angiotensin II were markedly suppressed, with a reciprocal rise in plasma renin. While plasma level of noradrenaline appeared to have fallen slightly, levels of adrenaline and anti-diuretic hormone were increased. **(Tables 13.1 & 13.2)**

TABLE 13.1
HAEMODYNAMIC AND NEUROENDOCRINE EFFECTS OF CAPTOPRIL IN A PATIENT DEVELOPING SYNCOPE AFTER 3MG OF CAPTOPRIL.

PATIENT 1

TIME		0mins BASELINE	40mins 1MG	40mins 2MG	40mins 3MG
HEART RATE	(bpm)	78	74	76	43
SYSTOLIC BP	(mmHg)	124	118	116	64
DIASTOLIC BP	(mmHg)	78	80	80	?
PUL.ART.DIA.P	(mmHg)	18	16	14	8
P.A.R.C.	(uU/ml)	84	72	170	1,236
P.ANG.II	(pmol/L)	27	21	25	?
PARC/P.ANG.II		3.1	3.4	6.8	?
P.NORADR.	(nmol/L)	4.3	4.1	4.6	2.8
P.ADRENALINE	(nmol/L)	0.3	0.3	0.3	5.3
P.A.D.H.	(pg/ml)	1.3	1.2	1.2	3.7

BP = blood pressure. Pul. Art.Dia. = pulmonary arterial diastolic
P = plasma. A.R.C. = active renin concentration.
Ang II = angiotensin II. Noradr = noradrenaline
A.D.H. = anti-diuretic hormone

TABLE 13.2
HAEMODYNAMIC AND NEUROENDOCRINE EFFECTS OF CAPTOPRIL IN A PATIENT DEVELOPING SYNCOPE AFTER 3MG OF CAPTOPRIL.

PATIENT 2

TIME		0mins BASELINE	40mins 1MG	40mins 2MG	35mins 3MG
HEART RATE	(bpm)	86	83	83	52
SYSTOLIC BP	(mmHg)	106	104	106	58
DIASTOLIC BP	(mmHg)	74	80	76	?
PUL.ART.DIA.	(mmHg)	36	34	34	18
P.A.R.C.	(uU/ml)	154	148	246	784
P.ANG.II	(pmol/L)	36	38	30	6
PARC/P.ANG.II		4.3	3.9	8.2	130.7
P.NORADR.	(nmol/L)	6.7	6.0	5.9	3.1
P.ADRENALINE	(nmol/L)	0.3	0.4	0.3	7.2
P.A.D.H.	(pg/ml)	1.9	1.7	2.1	5.9

For abbreviations see table 13.1

Both patients responded to the simple expedient of head-down tilt, and recovered fully in 5-10 minutes.

Both patients subsequently received several doses of 3 mg captopril, and although their blood pressures remained low, they did not develop symptomatic hypotension. After 48 hours, the patients were allowed up. Their clinical course thereafter was very satisfactory.

Although no haemodynamic effect occurred with the 1 and 2 mg doses of captopril, a small rise in plasma renin concentration was observed in both cases with the 2 mg dose of captopril, though no consistent fall in plasma angiotensin II occurred.

The ratio of plasma renin concentration to plasma angiotensin II increased, suggesting impaired negative feedback suppression of plasma renin by angiotensin II. This may reflect inhibition of locally synthesized angiotensin II, leading to increased renal renin secretion. Alternatively, it may indicate in the clinical setting a greater robustness of the renin assay.

CHAPTER 14: CAPTOPRIL IN HEART FAILURE: A DOUBLE-BLIND CONTROLLED TRIAL

Severe congestive cardiac failure entails a heavy burden of symptoms and carries a grave prognosis.

Captopril would be expected to have all the advantageous properties of conventional vasodilator agents in severe heart failure and also to have substantial additional benefits. Converting enzyme inhibition should overcome the possibly adverse direct renal effects of the renin-angiotensin system in severe heart failure as well as lowering secretion of anti-diuretic hormone and aldosterone.

Several open studies have indicated benefit from treatment with captopril; a double-blind trial is, however, critical in assessing the long-term effect of any drug in a disease with such prominent symptoms and fluctuating natural history. This study was one of the first three to report a beneficial effect of captopril in chronic heart failure[696,697] in a controlled trial. In addition to studying the effects of captopril on symptoms and exercise capacity in patients with heart failure, we also studied the effects on neuroendocrine activation, renal function, and the disturbed metabolism of heart failure.

PATIENTS AND METHODS

Fourteen men and 6 women (mean age 62 years) with severe congestive heart failure (New York Heart Association Class III or IV) of more than 6 months' duration were studied. Thirteen had ischaemic heart disease, 4 congestive cardiomyopathy, and 3 severe left ventricular dysfunction associated with valvar regurgitation. All were receiving digoxin together with frusemide (mean dose 375 mg/day); 3 were also receiving bendrofluazide 5 mg/day, and 2 others had been taking amiodarone 200 mg/day for more than a year. Six patients had atrial fibrillation. None had angina, significant respiratory disease, or serum creatinine concentrations >200 mol/l (2.26 mg/100ml). All gave written consent to the trial, which was approved by the hospital's ethical supervisory committee.

The study was in 4 phases, full patient assessment being performed at the end of each. Firstly, during a run-in phase of 2 weeks, treatment with digoxin, diuretics, potassium supplements, and amiodarone was stabilised and the patient made familiar with the procedures, including treadmill exercise. Secondly, captopril was introduced at a dose of 6.25 mg 3 times daily and titrated to a fixed thrice-daily dose for each patient (mean total dose 93.75 mg;range 37.5-150 mg) for an open study of 6 weeks' duration. Thirdly, patients were randomly allocated double-blind to receive either the same dose of captopril as in the second phase or a matching placebo for 6 weeks.

Fourthly, for a final 6 weeks, patients were crossed over double-blind to the alternative treatment to that given in the third phase. All treatment other than captopril was maintained without change throughout the third and fourth phases.

Symptoms were assessed according to the New York Heart Association classification, and by visual analogue scales for breathlessness, tiredness and ankle swelling. Exercise tolerance was tested with a modified Balke treadmill protocol in stages of 3 minutes. End- diastolic and end-systolic dimensions and fractional shortening were calculated from left ventricular M-mode echocardiographic monitoring. Twenty-four hour ambulatory electrocardiographic monitoring was performed using a Medilog I system. (See Methods - Chapter 7)

Venous blood samples were drawn at 8 am, the patients having fasted and remained supine overnight, 10 hours after the previous dose of captopril or placebo. Samples were assayed for serum concentrations of electrolytes, urea, creatinine, and for plasma concentrations of active renin, angiotensin II, aldosterone, cortisol, noradrenaline, and adrenaline. Blood pressure was measured between 2 pm and 4 pm with a standard sphygmomanometer lying and after 2 minutes standing; heart rate was recorded at the same time.

Total body potassium content was measured from endogenous ^{40}potassium, using the whole body counter; total body sodium, chlorine, calcium, phosphorus and nitrogen content were measured similarly after activation analysis.

Renal plasma flow and glomerular filtration rate were estimated with radioisotope clearance methods, using sodium iodohippurate (^{131}I) and ^{99m}technetium diethylenetriamine penta-acetic acid (DTPA). Urinary creatinine clearance over 24 hours was also measured.

The studies requiring nuclear medicine techniques were only performed during the double-blind part of the study.

STATISTICAL METHODS

The results of 3 analyses are presented, each based on standard statistical methods with the data transformed to a logarithmic scale as appropriate. The first comparison was between the start and finish for the open study and the second between the ends of the phases of the double-blind study during which placebo or captopril was given. The final comparison used repeated measures analyses of variance to incorporate data from the start of the double-blind study together with data from the end of the placebo and captopril phases, and, in effect, this compared the changes during the 2 double-blind 6- week periods of treatment. The design of the study shows that this final

analysis would be sensitive to any effect of the order of treatment allocation, and the results are not reported in cases where the order effect was significant at the 5% level.

RESULTS

Tables 14.1-14.4 give the results of all the tests undertaken.

CLINICAL OUTCOME

Of the 20 patients entered, 14 completed the study. Two died in the initial run-in phase, 2 during the open captopril phase, and one in the double-blind phase while taking placebo. The condition of a sixth patient with mitral incompetence improved considerably during the open captopril phase, and he was therefore withdrawn for valve replacement. The tables give detailed results only for the 14 patients who completed the study, unless otherwise stated.

SYMPTOMS

Breathlessness, tiredness, and New York Heart Association classification were all significantly improved in the double-blind captopril phase of the study; by contrast, ankle swelling was not. **(Table 14.1)**

TABLE 14.1
CLINICAL EFFECTS OF CAPTOPRIL COMPARED TO PLACEBO

SYMPTOMS	BASELINE	CAPTOPRIL OPEN	CAPTOPRIL DOUBLE BLIND	PLACEBO DOUBLE BLIND	
n = 14					
V.A.S.(mm)					
- BREATHLESSNESS	52(27)	15(12)	16(17)	34(22)	p<0.02
- TIREDNESS	48(25)	26(20)	12(14)	28(28)	p<0.02
- ANKLE SWELLING	20(25)	6(7)	6(8)	8(14)	ns
New York Heart Association Class					
- MEAN	3.5	2.0	2.0	2.5	
- MEDIAN	4	2	2	2	
- RANGE	3-4	1-3	1-3	2-4	p<0.02
WEIGHT (kg)	66.8(14.7)	66.1(10.2)	67.0(9.2)	67.0(9.1)	ns
SYSTOLIC BP(mmHg)	118(20)	109(16)	110(18)	130(27)	p<0.001
DIASTOLIC BP(mmHg)	79(14)	68(12)	64(13)	83(16)	p<0.001
HEART RATE(bpm)	83(9)	79(10)	75(11)	79(11)	*
EXERCISE TIME(secs)	336(228)	546(300)	549(318)	456(258)	p<0.007

* = order effect significant at the 5% level
VAS = visual analogue scores. BP = blood pressure

TABLE 14.2
THE EFFECTS OF CAPTOPRIL ON CARDIAC FUNCTION.

		BASELINE	CAPTOPRIL OPEN	CAPTOPRIL DOUBLE BLIND	PLACEBO DOUBLE BLIND	
ECHOCARDIOGRAPHY						
LEFT VENTRICULAR						
- DIMENSION (mm)						
- END-DIASTOLE		67(8)	64(12)	64(10)	67(10)	(p<0.06)
- END-SYSTOLE		56(11)	53(11)	52(10)	55(10)	p<0.04
- FRACTIONAL SHORTENING (%)		17.2(6.8)	18.3(5.9)	18.7(5.9)	17.3(5.6)	n.s.
AMBULATORY ELECTROCARDIOGRAPHY						
VENTRICULAR (in 24hours)						
- EXTRASYSTOLES	mean	3917	2353	1387	1897	
	median	187	107	121	199	
	range	3-24570	0-24299	0-10445	0-11416	p<0.05
- COUPLETS	mean	82	26	8	14	
	median	2	1	0	3	
	range	3-750	0-357	0-82	0-103	(p<0.06)
- SALVOES	mean	9	7	5	13	
	median	0	0	0	1	
	range	0-94	0-67	0-70	0-147	p<0.02
- TACHYCARDIA	mean	9	5	4	7	
	median	0	0	0	1	
	range	0-94	0-67	0-49	0-86	p<0.05

TABLE 14.3
BIOCHEMISTRY AND TOTAL BODY COMPOSITION

		BASELINE	CAPTOPRIL OPEN	CAPTOPRIL DOUBLE BLIND	PLACEBO DOUBLE BLIND	
n = 14						
SERUM CONCENTRATIONS						
- SODIUM	(mmol/L)	140(5)	141(3)	140(3)	140(6)	ns
- POTASSIUM	(mmol/L)	3.4(0.7)	3.9(0.6)	3.9(0.4)	3.4(0.4)	p<0.001
- CHLORIDE	(mmol/L)	100(5)	101(7)	99(5)	96(11)	ns
- CALCIUM	(mmol/L)	2.3(0.1)	2.3(0.1)	2.3(0.1)	2.3(0.1)	ns
- PHOSPHATE	(mmol/L)	1.0(0.2)	1.1(0.2)	1.1(0.2)	0.9(0.1)	p<0.02
- UREA	(mmol/L)	9.3(5.7)	10.8(9.7)	11.1(8.4)	7.7(3.6)	p<0.01
- CREATININE	(umol/L)	116(40)	123(45)	133(42)	113(32)	p<0.02
-WHITE CELL COUNT	(X10 /L)	8.1(1.4)	7.0(6.5)	6.3(1.3)	7.4(1.1)	ns
PLASMA CONCENTRATIONS						
- ACTIVE RENIN	(uU/ml)					
- mean		168	383	405	262	
- median		51	97	104	55	
- range		20-1209	28-2287	46-2289	12-501	*
- ANGIOTENSIN II	(pmol/L)					
- mean		53	22	21	80	
- median		36	22	17	31	
- range		8-178	4-38	6-47	10-292	p<0.01
- ALDOSTERONE	(pmol/L)					
- mean		924	252	308	504	
- median		336	196	224	280	
- range		112-2100	56-924	56-1568	84-2072	ns
- NORADRENALINE	(nmol/L)	4.1(2.1)	3.0(2.0)	3.2(1.7)	5.1(2.6)	p<0.05
- ADRENALINE	(nmol/L)	0.2(0.3)	0.2(0.3)	0.3(0.2)	0.5(0.4)	p<0.03
TOTAL BODY COMPOSITION						
- SODIUM	(mmol)		3195(437)	3195(447)	3200(367)	ns
E/P	(%)		104(11)	103(8)	104(7)	ns
- POTASSIUM	(mmol)		2596(443)	2667(111)	2543(135)	p<0.03
E/P	(%)		94(12)	97(14)	92(14)	
- CHLORINE	(mmol)		1604(263)	1627(245)	1600(239)	ns
E/P	(%)		100(7)	99(6)	97(11)	
- CALCIUM	(mmol)		23311(3287)	23264(2905)	23441(3199)	ns
E/P	(%)		106(13)	104(11)	104(11)	
- PHOSPHORUS	(mmol)		15953(2397)	16303(2025)	16241(2200)	ns

E/P = estimated/predicted

ADVERSE REACTIONS

Two patients developed morbiliform rashes within 2 weeks of starting captopril. Both were receiving doses at the upper limit for their level of renal function (captopril 300 mg/day, with creatinine clearances 48 and 43 ml/minute). The rashes cleared on stopping captopril, and in both patients the drug was started again at lower doses, without relapse. Two patients had mild postural dizziness without demonstrable hypotension on starting captopril; symptoms resolved spontaneously. Total white cell count showed a slight but significant decline ($p<0.05$) during the open phase of captopril. **(Table 14.2)** A similar trend in the double-blind phase was not significant. The lowest individual white cell count throughout the trial was 4000 x 10^6/l, with a normal differential count.

EXERCISE TESTING

Exercise time was significantly increased during double-blind captopril treatment **(Table 14.1)**

WEIGHT

With the initiation of captopril in the open phase, mean (SD) body weight rose over the first week from 66.3 (2.5) kg to 67.5 (2.6) kg ($n=18;p<0.05$). This was largely due to distinct retention of fluid in 5 patients, 2 of whom required an increase in frusemide dosage. There were thereafter no significant differences in body weight between the mean values at the end of each phase of the

study. **(Table 14.1)** Diuretics were fixed in the 4-week period prior to the double- blind part of the study. Diuretics were not changed during the double-blind study.

BLOOD PRESSURE AND HEART RATE

Both systolic and diastolic pressures, supine and standing, were lower during treatment with captopril; there was no postural fall in blood pressure in this study. Heart rate was not significantly changed in either posture. **(Table 14.1)**

ECHOCARDIOGRAPHY

Both end-systolic and end-diastolic dimensions were reduced by captopril, although fractional shortening was not increased. **(Table 14.2)**

TWENTY-FOUR HOUR AMBULATORY ECG MONITORING

The incidence of ventricular extrasystoles, couplets, ventricular salvoes, and ventricular tachycardia were all significantly lower with captopril. **(Table 14.3)**

SERUM ELECTROLYTES (Table 14.3)

Mean serum potassium on placebo and during the run-in period was low at 3.4 mmol l^{-1}. Two patients were

hyponatraemic with serum sodium of less than 128 mmol l^{-1}. Captopril caused a significant increase in serum potassium levels; the increase was directly related to plasma active renin concentration in the placebo phase ($r=0.61;p<0.05$). Despite correcting hyponatraemia in some patients, mean serum sodium did not change. Serum chloride and calcium did not change with captopril therapy. However, serum phosphate was significantly higher on captopril therapy.

HORMONES

Plasma active renin concentration was elevated in the placebo phase and was positively correlated to plasma angiotensin II ($r=0.92;p<0.001$). Angiotensin II was, in turn, positively related to plasma aldosterone and plasma noradrenaline.

With captopril therapy, plasma angiotensin II formation was suppressed, renin rose, while plasma aldosterone showed a statistically insignificant decline. Plasma noradrenaline and adrenaline also declined. **(Table 14.3)**

TOTAL BODY ELECTROLYTE COMPOSITION (Table 14.3)

Total Body Sodium

Absolute values and changes in total body sodium were not significantly correlated to plasma renin concentration. During the placebo phase, even in these oedema-free

patients, total body sodium was increased for the group as a whole. During treatment with captopril, total body sodium was unchanged on captopril, whether considered either as an absolute value or as a ratio to predicted normal.

Total Body Potassium

During the placebo phase, total body potassium was depleted for the group as a whole. Those patients with abnormally high plasma renin and angiotensin II concentrations had lower total body potassium levels $p<0.05$) than did those with normal plasma renin. Serum potassium correlated linearly with total body potassium ($r=0.82;p<005$). Captopril caused a significant rise in total body potassium, the mean difference in total body potassium between the captopril and placebo double-blind phases being 124 mmol. The increase in total body potassium was directly correlated with the highest plasma active renin concentration in the placebo phase ($r=0.58;p<0.05$).

Total Body Chlorine

During the placebo phase, total body chlorine was not significantly different from predicted at $992\pm12\%$. Whole body chlorine tended to be higher in those with normal plasma renin concentrations. These values were unaltered by captopril. Calculated extracellular fluid volume, even taking into account weight, tended to be lower in the low renin subgroup. Under the influence of captopril, there was a statistically insignificant de cline in mean

extracellular fluid volume.

Whole Body Nitrogen, Calcium and Phosphorus

During the placebo phase, whole body nitrogen, calcium and phosphorus did not differ significantly from predicted, indicating no abnormality of body habitus to account for the changes in total body potassium and sodium. The amounts of these elements were unaltered by captopril.

EFFECTS OF CAPTOPRIL ON RENAL FUNCTION

Detailed results on renal function are presented in Figures 14.1 and 14.2, & Table 14.4.

Serum urea, creatinine and phosphate increased significantly during the captopril phase of the study. Creatinine clearance fell with the administration of captopril, while radio-isotopically estimated glomerular filtration rate showed a similar but non-significant decline.

Effective renal plasma flow increased; therefore, calculated filtration fraction fell. Mean arterial pressure also fell and renal blood flow increased. Calculated reno-vascular resistance declined.

During the placebo phase, glomerular filtration rate was directly related to effective renal plasma flow ($r=0.95;p<0.001$), as expected. The change in glomerular

TABLE 14.4
RENAL FUNCTION - THE EFFECTS OF CAPTOPRIL

	BASELINE	CAPTOPRIL OPEN	CAPTOPRIL DOUBLE BLIND	PLACEBO DOUBLE BLIND	
n = 12					
G.F.R. (ml/min)			48(18)	53(19)	ns
CREATININE CLEARANCE (ml/min)	62(22)	56(20)	56(21)	61(21)	p<0.01
E.R.P.F. (ml/min)			287(100)	241(72)	p<0.05
SERUM DIGOXIN (mmol/L)	1.3(0.1)	1.6(0.2)	1.7(0.2)	1.4(0.1)	p<0.05

G.F.R. = GLOMERULAR FILTRATION RATE
E.R.P.F. = EFFECTIVE RENAL PLASMA FLOW

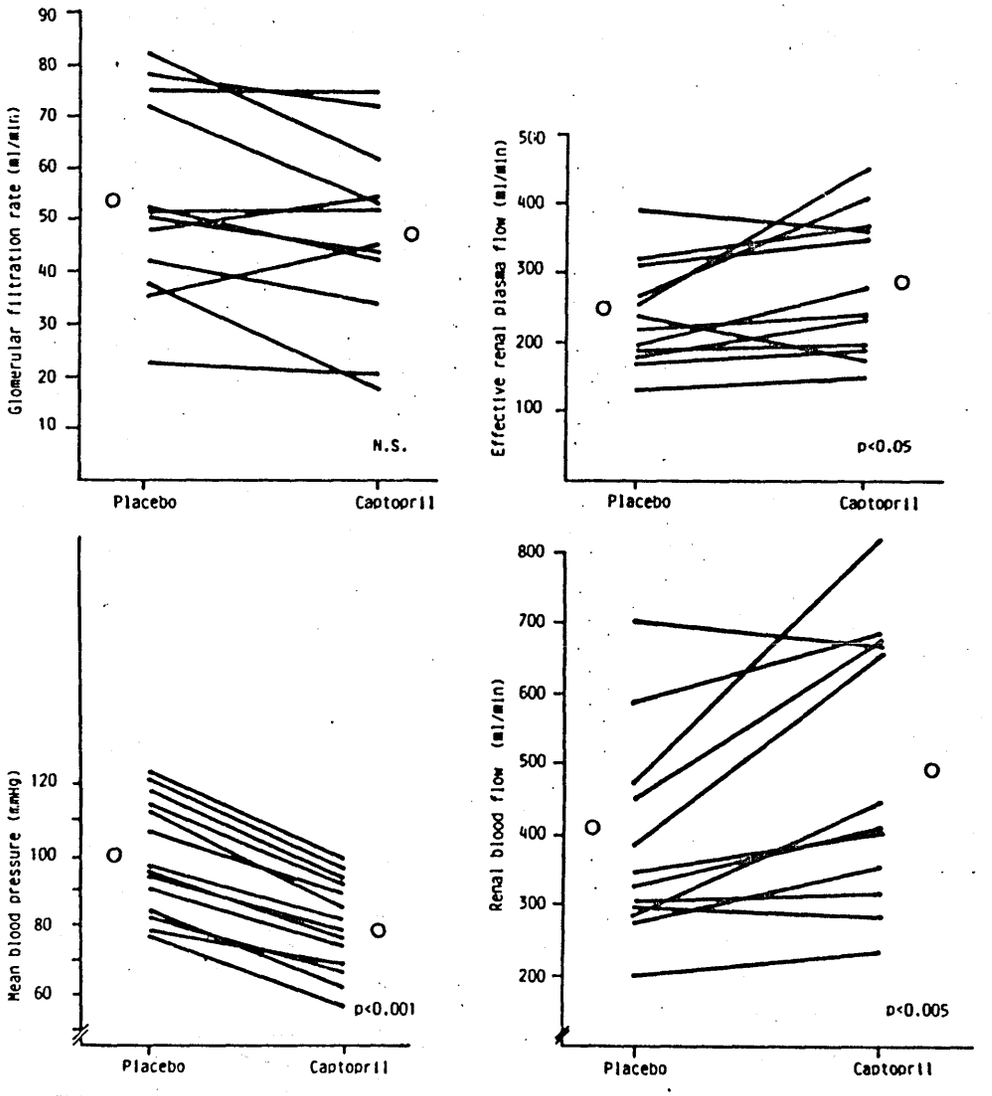


Figure 14.1 Individual (solid line) and mean (open circle) changes in glomerular filtration rate, effective renal plasma flow, renal blood flow, and mean blood pressure between double-blind placebo and captopril phases.

Figure 14.2 Individual (solid line) and mean (open circle) changes in serum creatinine and urea, filtration fraction, and renovascular resistance between double-blind placebo and captopril phases.

filtration rate with captopril was not related either to the percentage fall in mean blood pressure **(Figure 14.3)** or to blood pressure measured during either the placebo or captopril phase in this study. The patients in whom the greatest fall in glomerular filtration rate occurred were those in whom renal vascular resistance failed to decrease sufficiently to cause an adequate increase in effective renal plasma flow. **(Figure 14.4)**

No long-term natriuresis took place in our patients, since total body sodium did not change. This confirms the lack of natriuretic effect noted by others in open studies. That sodium balance was maintained in the face of the fall in glomerular filtration rate and blood pressure suggests that the natriuresis expected from the increase in renal blood flow was counterbalanced by the sodium-retaining effect of an overall fall in peripheral resistance and blood pressure. Despite this lack of long-term natriuresis, clinical improvement did occur, with a reduction of symptoms and improvement in exercise performance.

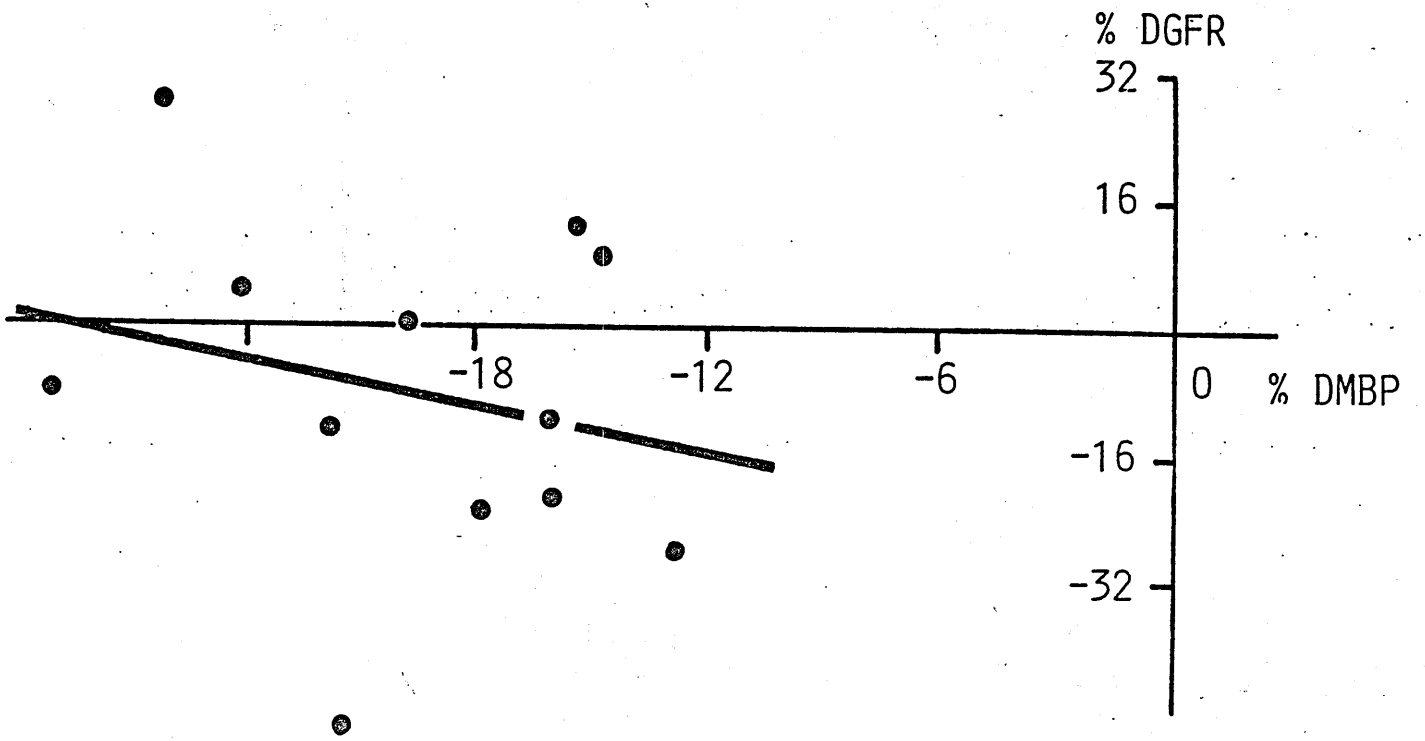


Figure 14.3 Poor relationship (r=-0.22;ns) between percentage change in mean blood pressure and percentage change in glomerular filtration rate between placebo and captopril phases.

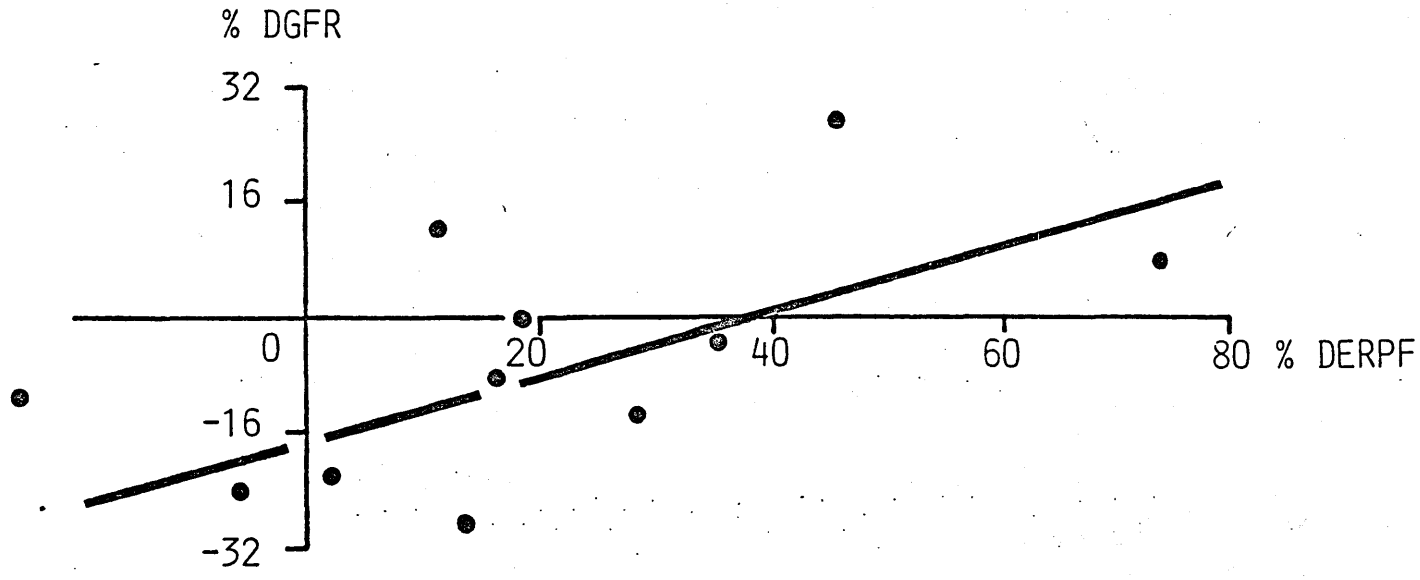


Figure 14.4 Relationship ($r=0.58; p<0.05$) between percentage change in effective renal plasma flow and percentage change in glomerular filtration rate between double blind placebo and captopril phases.

CHAPTER 15: EFFECTS OF ENALAPRIL IN HEART FAILURE: A DOUBLE-BLIND STUDY OF EFFECTS ON EXERCISE PERFORMANCE, RENAL FUNCTION, HORMONES AND METABOLIC STATE

INTRODUCTION

This study is similar in concept to the study described in Chapter 14, but included more detailed assessment of renal function in a slightly larger population of patients, with somewhat milder heart failure.

In addition to the assessments in Chapter 14, a much detailed investigation of the autonomic and neuroendocrine effects of angiotensin-converting enzyme therapy was carried out.

PATIENTS

We studied 20 patients with chronic heart failure caused by ischaemic heart disease (9), congestive (dilated) cardiomyopathy (8), or severe left ventricular dysfunction after successful valve replacement (3) who were in New York Heart Association class II or IV. Mean (SD) duration of symptoms at entry was 18 (13) months.All had had symptoms for more than 3 months. Patients with serious concomitant disease or appreciable valvar regurgitation were excluded. All vasodilators were withdrawn at least one month before investigation and doses of frusemide (mean (SD) daily dose 124 (57) mg/day) and digoxin (mean daily dose 0.22 (0.06 mg/day) were held constant. One patient refused frusemide

and continued on bumetanide 3 mg/day. Four patients were also on amiloride 10-15 mg/day, 5 on potassium chloride (1.8-2.4 g/day), one on hydrochlorthiazide 100 mg/day, and one had been treated with amiodarone 400 mg/day for the previous 2 years; doses of these agents were also held constant through the trial.

STUDY DESIGN

Patients were assessed and were familiarised with study procedures, including repeated exercise tests, 4 weeks before the start of the study. They were then admitted for 10 days for full initial assessment before being randomly allocated to enalapril 5 mg/day or matching placebo. Doses of enalapril (or matching placebo) were then doubled every 2 weeks to a maximum of 40 mg once daily (9 am) if no adverse effect occurred. After 2 months, patients were readmitted, reassessed, and then started on the alternative treatment. Doses were again doubled every 2 weeks and patients were finally assessed after a further 2 months in the trial.

METHODS

For more detailed discussion of the methods, see Chapter 7.Symptoms were evaluated by New York Heart Association score and by visual analogue scores for breathlessness, tiredness, and ankle swelling. Exercise capacity was measured by a modified Bruce protocol, with stages which lasted 3 minutes. Left ventricular internal dimensions were

derived from M-mode echocardiography and systolic time intervals from the aortic root echocardiogram. Ambulatory electrocardiographic monitoring was performed for 48 hours with a Medilog-I system and the results were expressed as events per 24 hours. Repetitive extrasystoles were defined as 3 or more consecutive ventricular extrasystoles. Blood pressure was measured with a Hawksley random zero sphygmomanometer, and heart rate was taken from the apex beat 6 hours after dosing.The QT interval was calculated from the resting ECG.

Venous blood was drawn at 9 am, 24 hours after dosing, from the patients who had fasted (apart from water), and had remained supine overnight. Further samples were taken at 1 pm, 4 hours after usual therapy and drug or placebo, with the patient resting in the supine position, then after 5 minutes standing, and subsequently immediately after a maximal exercise test.Samples were assayed for serum electrolytes, urea, and creatinine concentrations, and for plasma concentrations of active renin, angiotensin II, aldosterone, vasopressin, noradrenaline and adrenaline. A further sample was taken 5 minutes after exercise for potassium and catecholamines.

Tests of autonomic function were carried out 2-3 hours after drug or placebo administration.

Total body potassium was derived from endogenous ^{40}K by

means of a whole body counter, and total body sodium was similarly determined after neutron activation.Effective renal plasma flow and glomerular filtration rates were determined by single injection isotope techniques. Creatinine clearance was calculated from a 24 hour urine collection and serum creatinine.

STATISTICAL ANALYSES

Possible order and period effects or both were assessed by comparison of the differences between observations for the enalapril and placebo phases for the 2 groups by means of 2 sample t-tests. In cases were the order effect was not significant, we compared treatment effects by means of paired t-tests on the enalapril and placebo measurements and ignored the order of treatment.Correlations were calculated by Pearson's product-moment correlation coefficient and these were tested for significance by t-tests. The data were log transformed where appropriate.

For studies on neuroendocrine function the results of 3 analyses are presented:

1) The actual values obtained during each treatment period were compared.

2) The response to physiological manoeuvres was compared within each treatment phase. For instance, the heart rate response during placebo was analysed, as was the

heart rate response during the enalpril treatment phase.

3) The magnitude of the responses to physiological manoeuvres was then compared between treatment phases. Thus, the change in heart rate from lying to standing was compared during enalapril or placebo administration.

RESULTS

In 17 patients, the dose of enalapril was increased to a maximum of 40 mg/day, in 2 patients the dose was limited to 20 mg/day, and in one to 10 mg/day because of symptomatic hypotension, which also occurred in 2 patients on 40 mg/day. No severe hypotension was observed after the first dose in any patient. No patient failed to reach the maximum dose of placebo.Nineteen patients completed the study; one patient died suddenly during the placebo phase after showing an improvement in symptoms and exercise capacity on enalapril.

SYMPTOMS(Table 15.1)

New York Heart Association score improved **(Figure 15.1)** during treatment with enalapril. Breathlessness and tiredness also improved but ankle swelling, not a prominent complaint at the start of the study, was unchanged.

ADVERSE EFFECTS

TABLE 15.1
CLINICAL EFFECTS OF ENALAPRIL COMPARED TO PLACEBO.

	BASELINE	ENALAPRIL	PLACEBO	
n = 19				
V.A.S.(mm)				
- BREATHLESSNESS				
- mean	56	24	45	
- median	61	7	45	
- range	15-92	0-89	3-95	p<0.006
- TIREDNESS				
- mean	51	29	39	
- median	58	13	41	
- range	0-100	0-88	0-96	ns
WEIGHT (kg)	66(11)	67(11)	67(11)	ns
SYSTOLIC BP(mmHg)	117(22)	100(23)	121(24)	p<0.0001
DIASTOLIC BP(mmHg)	75(12)	62(11)	72(10)	p<0.001
HEART RATE(bpm)	79(12)	72(9)	76(10)	p<0.03
EXERCISE TIME(secs)	390(192)	642(144)	522(186)	p<0.01

* = order effect significant at the 5% level
V.A.S. = visual analogue scores
BP = blood pressure

Figure 15.1 *New York Heart Association functional class at baseline, after treatment with enalapril, and on placebo. The difference between placebo and enalapril treatments was significant ($p < 0{\cdot}05$) by a modified χ^2 test*

Class	*Baseline*	*Enalapril*	*Placebo**
4	2	0	2
3	14	3	9
2	4	15	8
1	0	2	0
Mean score	2·9	2·1	2·7

*One death.

Weight increased in the first week on enalapril (0.4 (0.8)kg;$p<0.05$), whereas there was no change after one week on placebo (-0.1(0.6) kg). One patient had weight gain with increased ankle swelling; the latter improved on continued therapy without alteration of diuretic dose. Weight was similar on placebo and enalapril at the end of both 2-month periods.

Adverse responses included hypokalaemia (serum potassium <3.5 mmol/l) in 8 patients on placebo; slight increases in transaminases, one patient on placebo (alanine transaminase 62 U/l) and one on enalapril (60 U/l); and a pronounced increase in serum urea (6.8 mmol/l to 12.0 mmol/l) and creatinine (127 umol/l to 202 umol/l) in one patient on enalapril who also had postural hypotension (standing blood pressure on placebo 98/74 mm Hg, and on enalapril, 66/54 mm Hg). No patient developed proteinuria or a blood dyscrasia.

Other possible adverse effects were a mild persistent dry cough in one patient on enalapril. Transient skin eruptions were noted in 3 patients on enalapril (one case each of varicose eczema and 2 cases of a macular rash of hands and feet), and 2 on placebo (one case of varicose eczema and one of urticaria). In addition, one patient developed thoracic herpes zoster during enalapril therapy, from which she made an uncomplicated recovery. One patient, who had previously had a raised fasting blood glucose (8 mmol/l at baseline), developed glycosuria and a further increase in

his fasting blood glucose on enalapril (placebo 11.9 mmol/l; enalapril 13.4 mmol/l), which he had received after placebo.

CLINICAL VARIABLES(Table 15.1)

Exercise Testing (Table 15.1)

Exercise performance improved onage by one treadmill stage during enalapril treatment.

Blood Pressure and Heart Rate

Both systolic and diastolic blood pressure were significantly reduced on enalapril, and heart rate also declined. **(Table 15.1)**

Left Ventricular Function(Table 15.2)

Echocardiographic left ventricular systolic and diastolic dimensions were reduced by enalapril, although fractional shortening did not increase significantly.The ratio of pre-ejection period to left ventricular ejection time was also reduced, indicating an improvement in ventricular function.

Ambulatory Monitoring (Table 15.2)

Ventricular extrasystoles were significantly reduced (by 50%) during enalapril treatment, but the reduction in repetitive extrasystoles was not statistically significant.

TABLE 15.2
THE EFFECTS OF ENALAPRIL ON CARDIAC FUNCTION.

		BASELINE	ENALAPRIL	PLACEBO	
ECHOCARDIOGRAPHY					
LEFT VENTRICULAR					
- DIMENSION (mm)					
- END-DIASTOLE		69(10)	66(9)	69(9)	p<0.004
- END-SYSTOLE		58(12)	54(10)	58(12)	p<0.003
- FRACTIONAL SHORTENING (%)		16(7)	18(7)	17(6)	ns
- PEP/LVET (X1000)		667(204)	534(186)	631(172)	p<0.03
AMBULATORY ELECTROCARDIOGRAPHY					
VENTRICULAR (in 24hours)					
- EXTRASYSTOLES	mean	1702	1268	2140	
	median	555	560	659	
	range	15-11045	17-7827	17-9130	p<0.05
- VENTRICULAR SALVOES	mean	4.6	3.9	4.7	
	median	1	1.5	1	
	range	0-41	0-35	0-58	ns

Effect of Enalapril on QTC

At baseline, QTC measured 438±30 milliseconds and did not change during placebo therapy at 434±36 milliseconds. However, during therapy with enalapril, QTC was reduced at 415±44 milliseconds ($p<0.05$). QRS duration and the uncorrected QT interval were unchanged during any of the treatments.

Autonomic Function Testing (Table 15.3)

Baseline tests of autonomic function were abnormal, as outlined previously. Comparing placebo with enalapril, a greater fall in systolic blood pressure and rise in heart rate occurred after 2 minutes standing during enalapril therapy. The absolute levels of the penultimate heart rate and systolic blood pressure (ie the heart rate at the end of the last completed stage during the shorter of the two tests) were reduced by enalapril, but the change in each from rest to exercise was similar. The change in heart rate from rest to peak exercise was, in fact, greater during enalapril therapy.

Enalapril tended to normalise the heart rate response to the Valsalva manoeuvre, deep breathing, and the immediate heart rate response to standing.

Hormone Assays (Table 15.4-15.6)

At baseline, as expected and previously discussed, in

TABLE 15.3

AUTONOMIC FUNCTION TESTS (also see tables 15.1-15.6)

		BASELINE	ENALAPRIL	PLACEBO	
HEART RATE RESPONSE TO					
DEEP BREATHING	(bpm)	6.4(2.9)	14.3(6.1)	7.3(2.7)	p<0.001
VALSALVA RATIO	(bpm)	1.03(0.09)	1.18(0.10)	1.05(0.06)	p<0.005
15:30 RATIO	(bpm)	0.98(0.03)	1.03(0.04)	0.99(0.02)	p<0.05

TABLE 15.4
BIOCHEMISTRY

		BASELINE	ENALAPRIL	PLACEBO	
n = 19					
SERUM CONCENTRATIONS					
- SODIUM	(mmol/L)	139(4)	138(4)	139(3)	ns
- POTASSIUM	(mmol/L)	3.8(0.3)	4.2(0.3)	3.7(0.3)	p<0.0001
- MAGNESIUM	(mmol/L)	0.76(0.18)	0.84(0.08)	0.82(0.08)	p<0.05
- BICARBONATE	(mmol/L)	30(3)	28(3)	29(2)	p<0.05
- CHLORIDE	(mmol/L)	99(3)	99(4)	99(4)	ns
- CALCIUM	(mmol/L)	2.3(0.1)	2.3(0.3)	2.3(0.1)	ns
- PHOSPHATE	(mmol/L)	1.13(0.20)	1.19(0.15)	1.09(0.14)	p<0.001
- UREA	(mmol/L)	6.4(2.0)	8.0(2.4)	6.4(1.9)	p<0.001
- CREATININE	(umol/L)	100(24)	110(31)	101(24)	p<0.01
- URATE	(mmol/L)	0.46(0.10)	0.48(0.09)	0.47(0.10)	ns
- DIGOXIN	(nmol/L)	1.5(0.7)	1.8(0.8)	1.4(0.7)	p<0.01
PLASMA CONCENTRATIONS					
- ACTIVE RENIN	(uU/ml)				
- mean		81	695	98	
- median		47	406	61	
- range		3-352	3-2256	3-673	p<0.001
- ANGIOTENSIN II	(pmol/L)				
- mean		34	14	34	
- median		29	13	29	
- range		1-83	4-35	1-83	p<0.005
- ALDOSTERONE	(pmol/L)				
- mean		505	361	578	
- median		361	289	325	
- range		217-1336	144-1408	181-3069	p<0.05
- ANTI-DIURETIC HORMONE	(pg/ml)				
- mean		1.9	1.3	2.2	
- median		1.6	1.1	1.5	
- range		0.3-5.1	0.2-3.6	0.5-7.8	p<0.02
- NORADRENALINE	(nmol/L)	3.2(1.4)	2.2(0.8)	3.2(1.2)	p<0.002
- ADRENALINE	(nmol/L)	0.3(0.1)	0.3(0.2)	0.4(0.2)	ns

VALUES ARE MEAN (STANDARD DEVIATION) UNLESS OTHERWISE STATED

TABLE 15.5
NEUROENDOCRINE EFFECTS OF ENALAPRIL BEFORE AND AFTER TREATMENT WITH DIURETIC AND DIGOXIN.

		BASELINE	ENALAPRIL	PLACEBO	
SUPINE FASTING					
Heart Rate (bpm)		79(10)	72(9)	78(10)	p<0.01
Sys BP (mmHg)		119(26)	104(25)	122(23)	p<0.001
P.Potassium(mmol/L)		3.8(0.3)	4.3(0.3)	3.8(0.3)	p<0.001
P.Sodium (mmol/L)		139(3)	138(3)	139(3)	ns
P.A.R.C. (uU/ml)					
mean:median		81: 47	695:406	98: 61	
range		3-352	3-2256	3-673	p<0.001
P.Ang.II (pmol/L)					
mean:median		39: 31	14: 13	34: 29	
range		1-160	4-35	1-83	p<0.005
P.Aldo. (pmol/L)					
mean:median		505:361	361:289	578:325	
range		217-1336	144-1408	181-3069	p<0.05
P.A.D.H (pg/ml)					
mean:median		1.9:1.6	1.3:1.1	2.2:1.5	
range		0.3-5.1	0.2-3.6	0.5-7.8	p<0.02
P.N.Adr (nmol/L)		3.2(1.4)	2.2(0.8)	3.2(1.2)	p<0.002
P.Adr (nmol/L)		0.3(0.1)	0.3(0.2)	0.4(0.2)	
SUPINE AFTER THERAPY					
Heart Rate (bpm)		80(12)	71(9)	83(14)	p<0.005
Sys BP (mmHg)	@@	117(22)	99(26)*	124(24)	p<0.001
P.Potassium(mmol/L)	@@	3.5(0.3)***	4.2(0.4)	***3.4(0.4)	p<0.001
P.Sodium (mmol/L)	@	138(3)*	137(3)*	*138(3)	p<0.05
P.A.R.C. (uU/ml)				p<0.001	
mean:median	@@	152: 91	2627:1512	169: 94	
range		3-972**	3-9240***	*5-1360	p<0.001
P.AngII (pmol/L)					
mean:median	@@	55: 46	9: 8	52: 47	
range		1-134**	1-18*	**1-126	p<0.001
P.Aldo. (pmol/L)					
mean:median	@@	650:469	325:181	578:469	
range		108-1949**	144-1516	72-2130	p<0.001
P.A.D.H. (pg/ml)					
mean:median		2.2:1.9	1.4:1.2	2.0:1.9	
range		0.3-5.9	0.2-3.6	0.7-5.8	p<0.05
P.N.Adr (nmol/L)	@@	3.9(1.4)**	2.5(1.0)	*3.9(1.6)	p<0.005
P.Adr (nmol/L)		0.4(0.2)	0.3(0.2)	0.5(0.4)	ns

Comparisons have been made in three ways (see text for details):-
1) actual values results shown in right hand column
2) Within treatment comparisons. * = p<0.05, ** = p<0.01, *** = p<0.001
3) Between treatment comparisons. @ = p<0.05, @@ = p<0.01
For abbreviations see table 9.1

TABLE 15.6
NEUROENDOCRINE EFFECTS OF ENALAPRIL DURING STANDING AND EXERCISE.

	BASELINE	ENALAPRIL	PLACEBO	
STANDING (5 MINUTES)				
Heart Rate (bpm) @	84(14)	77(10)**	83(13)	p<0.01
Sys BP (mmHg) @@	118(19)	94(28)**	**124(24)	p<0.001
P.Potassium(mmol/L)	3.6(0.3)	4.2(0.3)	3.6(0.4)	p<0.0001
P.Sodium (mmol/L)	138(3)	138(3)	138(3)	ns
P.A.R.C. (uU/ml)				
mean:median	183:103	2869:1820	165:96	
range	4-1356	5-13510*	5-1025	p<0.001
P.Ang.II (pmol/L)				
mean:median	54: 40	8: 8	59:55	
range	7-156	2-16	4-150	p<0.001
P.Aldo. (pmol/L)				
mean:median	686:505	289:217	686:433	
range	108-2527	72-939	253-2419	p<0.001
P.A.D.H (pg/ml)				
mean:median	2.2:2.1	1.5:1.3	1.8:1.6	
range	0.3-6.5	0.2-3.2	0.2-5.3	ns
P.N.Adr (nmol/L) @@	4.1(1.5)	3.6(1.4)***	3.8(1.9)	ns
P.Adr (nmol/L)	0.3(0.3)	0.3(0.2)	0.3(0.3)	ns
IMMEDIATE POST-EXERCISE				
Heart Rate (bpm) @@	121(17)***	131(20)***	**126(13)	ns
Sys BP (mmHg)	149(27)**	141(33)**	**158(30)	p<0.005
P.Pot. (mmol/L)	3.8(0.3)***	4.5(0.4)**	***3.9(0.4)	p<0.01
P.Sodium(mmol/L) @	139(3)*	138(3)	*139(3)	p<0.05
P.A.R.C. (uU/ml)				
mean:median @@	219:183	3907:3034	192:122	
range	4-1443**	7-14140**	**7-862	p<0.001
P.AngII (pmol/L)				
mean:median @@	81:57	12:10	86:97	
range	10-183**	1-33*	**7-192	p<0.001
P.Aldo. (pmol/L)				
mean:median	975:578	505:397	903:578	
range	289-3032***	108-1408***	***433-2419	p<0.001
P.A.D.H. (pg/ml)				
mean:median	7.5:3.4	4.4:3.8	4.7:3.5	
range	0.6-57***	0.6-20.3**	**1.1-15.8	ns
P.N.Adr (nmol/L)	8.4(4.0)***	9.9(5.7)***	***9.4(5.9)	ns
P.Adr (nmol/L)	0.5(0.5)**	0.5(0.3)**	*0.5(0.5)	ns
FIVE MINUTES AFTER EXERCISE				
P.Pot. (mmol/L) @@	3.2(0.5)**	4.2(0.6)	**3.3(0.4)	p<0.001
P.Sodium (mmol/L)	138(3)	138(3)	138(3)	ns
P.N.Adr (nmol/L) @	7.4(4.6)	5.2(2.1)*	8.0(3.8)	p<0.01

patients with treated heart failure plasma levels of active renin, angiotensin II, aldosterone, noradrenaline, and anti-diuretic hormone were all significantly elevated and increased further after administration of the patient's usual therapy, consisting diuretic and digoxin.

No further increase in noradrenaline or other neuroendocrine variables was seen with standing. During exercise, patients with heart failure had further marked activation of all neuroendocrine systems.

After 8 weeks' therapy with enalapril, plasma angiotensin II levels were suppressed, as were plasma levels of aldosterone, noradrenaline and anti-diuretic hormone in the supine, fasting state and twenty-four hours after the last dose of enalapril. There was a reciprocal rise in plasma levels of active renin.

Four hours after a subsequent dose of enalapril together with diuretic and digoxin, there was a four-fold increase in plasma active renin, and a further significant suppression of plasma angiotensin II. In contrast to subjects at baseline and on placebo, there was a further fall in plasma aldosterone, despite the fact that a further dose of diuretic had been given.The rise in plasma noradrenaline seen after diuretic administration was also suppressed by enalapril.

After 5 minutes standing, little change occurred in plasma levels of renin, angiotensin II or anti-diuretic hormone. This was also true of plasma noradrenaline during the baseline and placebo phases. However, there was a significant rise in plasma noradrenaline after standing during enalapril therapy. This paralleled the rise in noradrenaline seen during standing in normal subjects.

During exercise, there was a significant rise in plasma levels of active renin, angiotensin II, aldosterone, noradrenaline and anti-diuretic hormone, both in the baseline and placebo phases. The increase in angiotensin II during exercise was prevented by enalapril, and there was an enhanced increase in plasma concentrations of active renin. The increase in plasma levels of aldosterone, noradrenaline and anti-diuretic hormone during exercise were not inhibited by enalapril.

Five minutes after exercise, plasma levels of noradrenaline were significantly lower after enalapril compared to placebo and baseline.

Electrolytes(Figure 15.2)

At baseline and on placebo, mean serum potassium and magnesium were at the lower limit of normal. There was a significant increase in serum potassium and magnesium on enalapril.

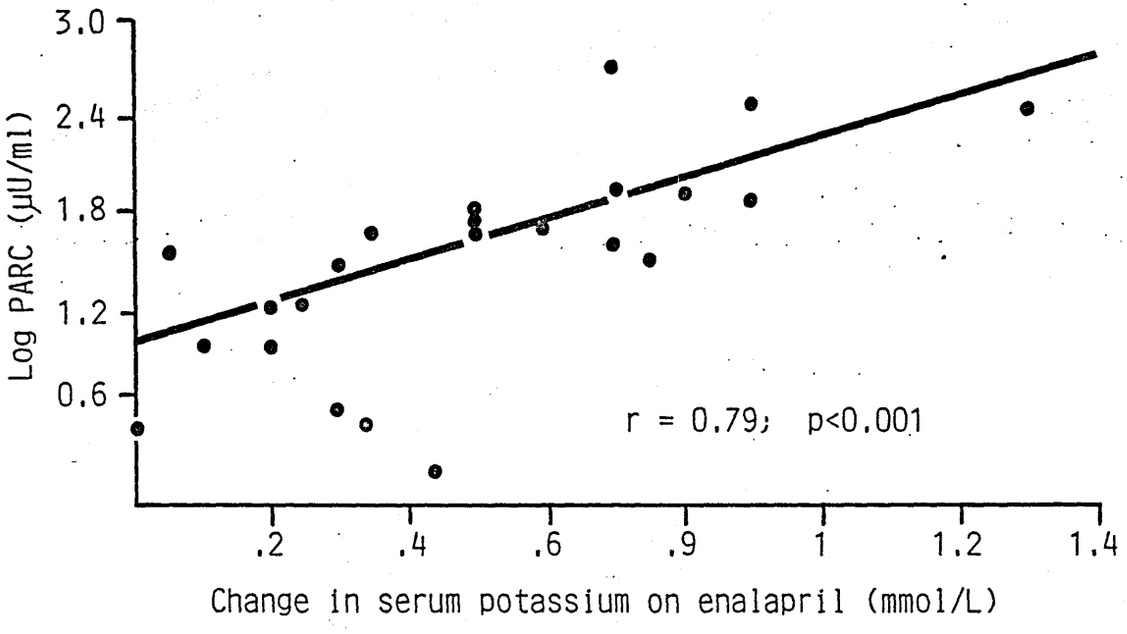


Figure 15.2 Relationship between the increase in serum potassium on enalapril and the baseline plasma renin concentration.

Initial serum potassium was inversely related ($r=-0.53; p<0.05$), and the rise in serum potassium on enalapril directly related ($r=0.79; p<0.001$), to the initial plasma renin concentration. **(Figure 15.2)**

No overall change in serum sodium occurred, nor was the fall in plasma sodium that occurred after diuretic therapy inhibited by enalapril. Two patients who developed postural hypotension (standing blood pressure on placebo 96/66 mm Hg & 108/88 mm Hg, falling to 72/56 mm Hg & 68/44 mm Hg, respectively, on enalapril), became hyponatraemic (serum sodium on placebo 139 mmmol/l & 134 mmol/l, and on enalapril 134 mmol/l and 121 mmol/l, respectively). These patients showed an increase in plasma ADH, rather than the fall seen in other patients.Two patients had hyponatraemia corrected on enalapril, serum sodium rising from 129 mmol/l & 134 mmol/l to 133 mmol/l and 137 mmol/l, respectively. During the baseline and placebo phases, the administration of diuretic therapy led to an acute fall in serum potassium. This was prevented by enalapril.Standing had no significant effect on plasma electolytes. However, during exercise there was an acute increase in potassium during all phases of the study and a small increase in plasma sodium during baseline and placebo phases only.

Five minutes after exercise, plasma potassium had fallen below supine basal levels. This was prevented by enalapril.

Serum bicarbonate fell during enalapril therapy, consistent with the correction of hypokalaemia. Serum chloride and calcium and urate were unchanged, but serum phosphate increased, consistent with a reduction in glomerular filtration rate.

Total Body Electrolytes (Table 15.7)

At baseline, total body potassium was low at 96±13% (mean ±standard deviation) of predicted normal values ($p<0.05$), while total body sodium was elevated at 108±11% ($p<0.01$). Total body chlorine, nitrogen, calcium, phosphorus and oxygen content did not differ from predicted normal values.

During treatment with enalapril, total body potassium increased and total body sodium decreased, though neither change was statistically significant. However, the ratio of total body sodium to total body potassium was markedly altered. Total body potassium was negatively correlated to plasma active renin concentration measured at baseline ($r=-0.64;p<0.01$).Changes in total body potassium were related to initial plasma renin concentration ($r=0.5;p<0.05$). **(Figure 15.3)**

TABLE 15.7
THE EFFECTS OF ENALAPRIL ON TOTAL BODY ELEMENTAL COMPOSITION

n = 16		BASELINE	ENALAPRIL	PLACEBO	
- SODIUM	(mmol)	3385(621)	3267(512)	3390(575)	ns
E/P	(%)	110(11)	106(11)	108(12)	
- POTASSIUM	(mmol)	2659(619)	2787(635)	2741(669)	ns
E/P	(%)	96(13)	99(12)	97(13)	
- POTASSIUM/SODIUM	(%)	79(12)	86(11)	81(11)	p<0.01
- CHLORINE	(mmol)	1760(392)	1751(278)	1797(311)	ns
E/P	(%)	109(16)	101(29)	104(30)	
- CALCIUM	(mmol)	24025(4013)	23933(4218)	23445(4243)	ns
- PHOSPHORUS	(mmol)	16889(2939)	16553(3134)	16738(2773)	ns
- NITROGEN	(g)	1632(323)	1666(325)	1619(311)	ns
E/P	(%)	106(16)	108(19)	105(17)	
- POTASSIUM/NITROGEN	(mmol/g)	1.63(0.17)	1.70(0.18)	1.68(0.16)	ns
- OXYGEN	(kg)	35.7(7.0)	36.4(6.6)	36.7(5.5)	ns

E = ESTIMATED P = PREDICTED.

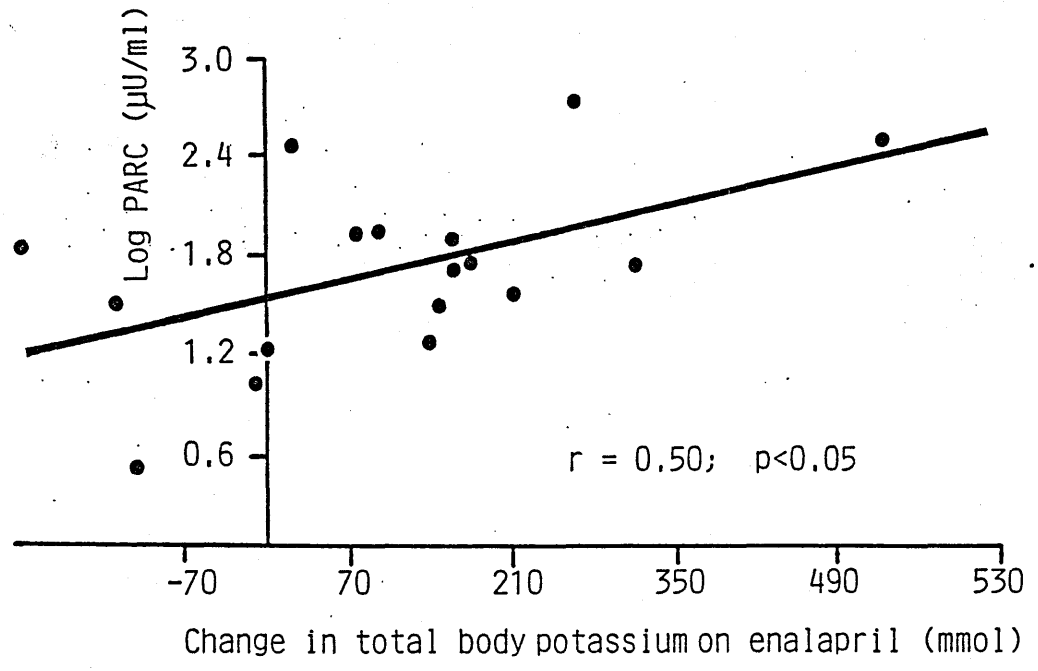


Figure 15.3 Relationship between the change in total body potassium on enalapril and the log of the plasma renin concentration.

Renal Function(Tables 15.8 & 15.9; Figures 15.4, 15.5 & 15.6)

In addition to measuring glomerular filtration rate and renal blood flow at baseline and at the end of each study periods, measurements were also taken at the end of the first week fo each double-blind period to help differentiate between short- and long-term effects on renal function.

During enalapril treatment, glomerular filtration rate measured isotopically was reduced and creatinine clearance also fell significantly, whereas effective renal plasma flow increased. The decline in glomerular filtration rate was reflected in a rise in serum urea and creatinine. The decline in glomerular filtration rate correlated with the decline in mean arterial pressure **(Figure 15.3)**, but not with the baseline plasma angiotensin II. **(Figure 15.4)**

Glomerular filtration rate was significantly depressed after one week of treatment, with a further significant decline at 8 weeks **(Table 15.9, Figure15.6)**. One week after withdrawal of enalapril, glomerular filtration rate had returned to normal. In contrast, renal blood flow was equally increased after one and 8 weeks of treatment and remained elevated after one week's withdrawal of therapy. Plasma angiotensin II was equally suppressed after one and 8 weeks treatment with enalapril, and was no different one week and 8 weeks after withdrawal.

TABLE 15.8
THE EFFECTS OF CHRONIC ENALAPRIL THERAPY ON RENAL FUNCTION

		BASELINE	ENALAPRIL	PLACEBO	
MEAN ARTERIAL PRESSURE	(mmHg)	94(16)	78(21)	94(15)	p<0.001
G.F.R.	(ml/min)	70(25)	58(23)	71(23)	p<0.0001
CREATININE CLEARANCE	(ml/min)	69(29)	65(24)	72(23)	p<0.04
E.R.P.F.	(ml/min)	289(101)	354(128)	308(119)	p<0.01
HAEMATOCRIT	(%)	42(5)	39(3)	40(5)	ns
RENAL BLOOD FLOW	(ml/min)	486(159)	578(226)	514(208)	p<0.02
RENAL VASCULAR RESISTANCE ((dynes/sec/cm)10)		16.3(5.9)	11.7(4.2)	16.6(6.1)	p<0.005
FILTRATION FRACTION	(%)	25.8(5.2)	17.0(4.8)	23.4(5.2)	p<0.0001

G.F.R. = GLOMERULAR FILTRATION RATE
E.R.P.F. = EFFECTIVE RENAL PLASMA FLOW

Table 15.9 Comparative effects of short- and long-term administration of enalapril on renal function in patients with heart failure.

	ONE WEEK OF THERAPY WITH ENALAPRIL	SIGNIFICANCE VERSUS 8 WEEKS PLACEBO	ENALAPRIL
MEAN ARTERIAL PRESSURE (mmHg)	90+18	p<0.05	p<0.001
GLOMERULAR FILTRATION RATE (ml/min)	62+19	p<0.01	p<0.005
CREATININE CLEARANCE (ml/min)	-----	-----	-----
EFFECTIVE RENAL PLASMA FLOW (ml/min)	320+84	p<0.001	n.s.
HAEMATOCRIT (%)	38+4	p<0.01	p<0.05
RENAL BLOOD FLOW (ml/min)	530+150	p<0.05	n.s.
RENAL VASCULAR RESISTANCE ((dynes/sec/cm)x10)	13.6+5.0	p<0.02	p<0.05
FILTRATION FRACTION (%)	19.6+4.0	p<0.001	p<0.01

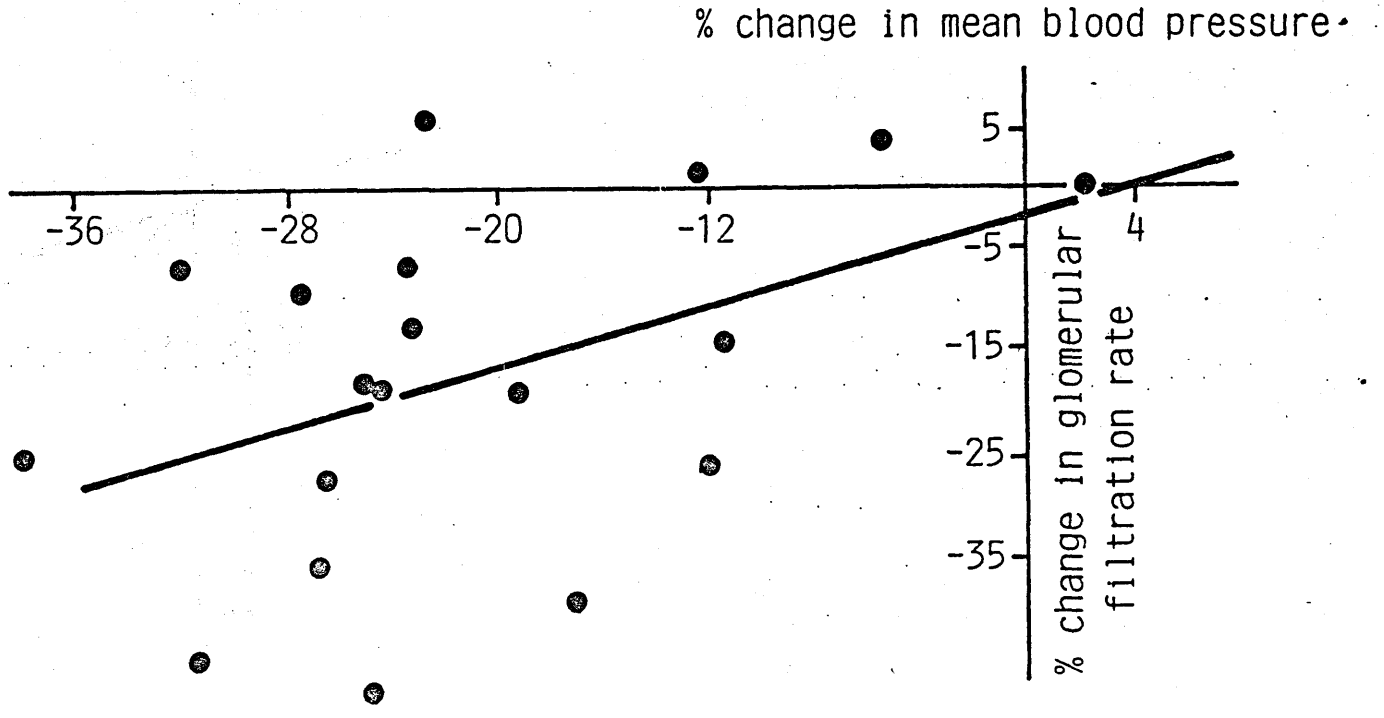


Figure 15.4 Relationship of the percentage change in mean blood pressure and the percentage fall in glomerular filtration rate during treatment with enalapril ($r=0.48$; $p<0.05$).

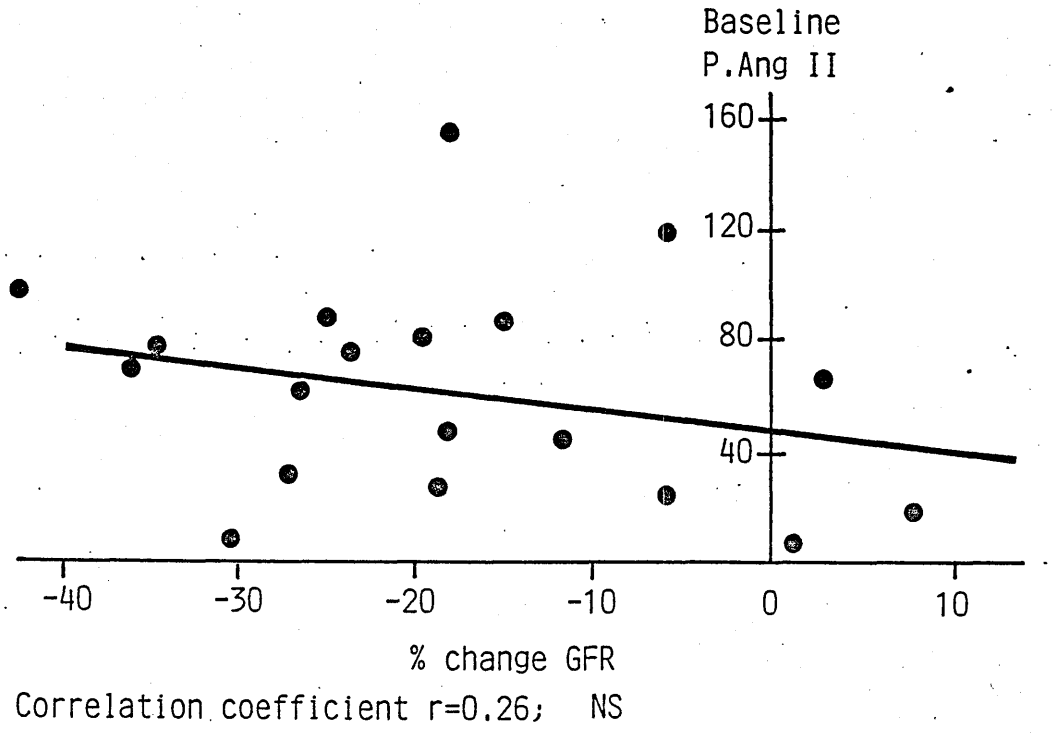
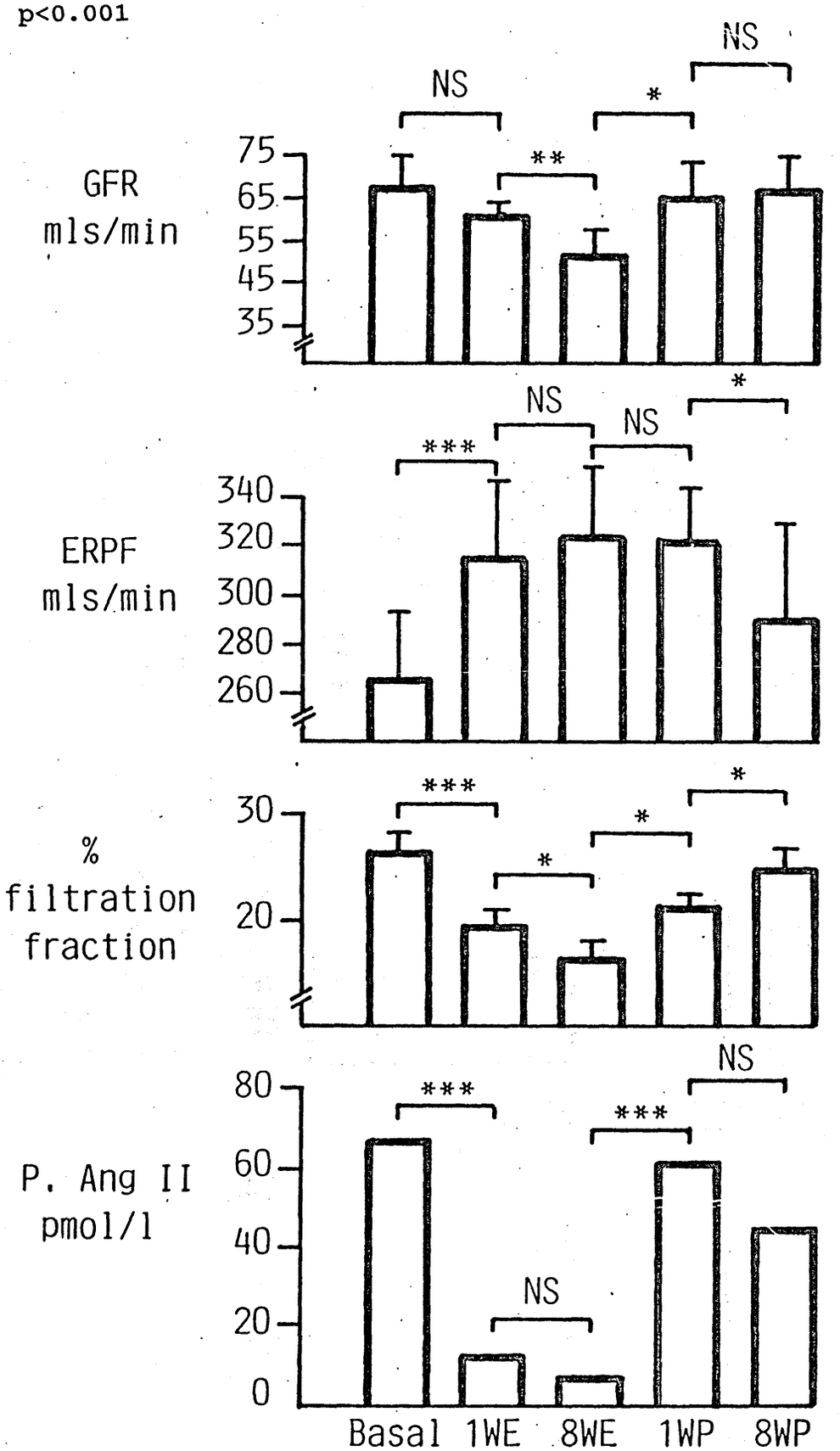


Figure 15.5 Relationship of the decline in glomerular filtration rate on enalapril to the initial plasma angiotensin II concentration (r=0.26;ns).

Figure 15.6 Effects of enalapril on renal function (mean ±standard deviation or median values in the case of plasma angiotensin II). * = p<0.05; **=p<0.01; ***= p<0.001



CHAPTER 16: THE EFFECTS OF FRUSEMIDE AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND THEIR COMBINATION ON CARDIAC AND RENAL HAEMODYNAMICS IN HEART FAILURE

Diuretics have formed the mainstay of medical therapy for heart failure for the last 30 years. While the efficacy of long-term digoxin therapy for patients with heart failure remaining in sinus rhythm is still under debate[698,699], angiotensin-converting enzyme inhibitors are now becoming accepted as effective second-line agents. However, there are important reasons for believing that angiotensin-converting enzyme inhibitors may not be valuable in the management of milder heart failure or as first-line agents,[700] reinforced by the finding that sodium retention may occur in normal subjects given captopril alone.[701]

It is likely that the combination of a diuretic, usually a loop diuretic, and angiotensin-converting enzyme inhibitor will form the accepted therapy for moderate to severe heart failure in the foreseeable future. Little is known of the combined effects of these 2 types of agent on cardiovascular and renal function in patients with heart failure. Frusemide, a standard loop diuretic, might interact in at least 3 possible ways with angiotensin-converting enzyme inhibitors. Firstly, acute administration of frusemide causes renin release, a phenomenon which appears independent of its other effects

and is prostaglandin-dependent.[702] Secondly, frusemide is a vaso-active compound, causing a decrease in venous tone[703] and a rise in renal blood flow[704] when given acutely. These effects may also be inhibited by indomethacin.[705,706] The effects on systemic vascular resistance and cardiac output seem more variable[703,707] and may depend on the clinical setting in which heart failure occurs. Frusemide may also cause a redistribution in renal blood flow.[708,709] Thirdly, due to the diuresis and fall in circulating volume, or possibly to local renal effects, it may stimulate the renin-angiotensin-aldosterone system, the sympathetic nervous system and plasma anti-diuretic hormone.[705,710] This neuroendocrine response may result in a rise in systemic vascular resistance and left ventricular filling pressures, and a fall in cardiac output in the setting of left ventricular failure. It has previously been shown that angiotensin-converting enzyme inhibitors not only reduce plasma angiotensin II in patients with heart failure, but also reduce plasma levels of aldosterone, noradrenaline and anti-diuretic hormone. Accordingly, the cardiac, renal and neuroendocrine effects of orally administered frusemide in patients with heart failure before and after one week of therapy with enalapril were investigated.

PATIENTS

Written, informed consent was obtained from 12 patients (mean age 58 ±11 years) with heart failure due primarily to left ventricular dysfunction. Two patients were women. The

aetiology was ischaemic heart disease in 8 patients and idiopathic dilated (congestive) cardiomyopathy in 4. All patients had received digoxin and diuretics for at least 3 months prior to investigation. The median dose of digoxin was 0.25 mg day^{-1} (range 0.125-0.375 mg day^{-1}), and of frusemide 120 mg day^{-1} (range 80-240 mg day^{-1}). Eight patients were in New York Heart Association Class III and 4 in Class IV. All patients were in sinus rhythm and were selected as having adequate recordings of aortic flow velocities by Doppler echocardiography from the cardiac apex.

All patients were commenced on a 100 mmol sodium and 40 mmol potassium diet, with 2500 ml total fluid intake for 48 hours prior to the study and for the 9 days of the study period. In order to achieve accurate dietary balance the patient was required to eat an identical diet each day for the duration of the study.

STUDY DESIGN

Patients were admitted to the ward and commenced on the above diet 48 hours before the study. Cardiac and renal haemodynamics were then studied in the presence or absence of a diuretic on separate days, at the same time of day, on days 3 and 4. **Figure 16.1)** Patients were then commenced on enalapril, and studies repeated in the presence of absence of a diuretic, on days 10 and 11.

Study design

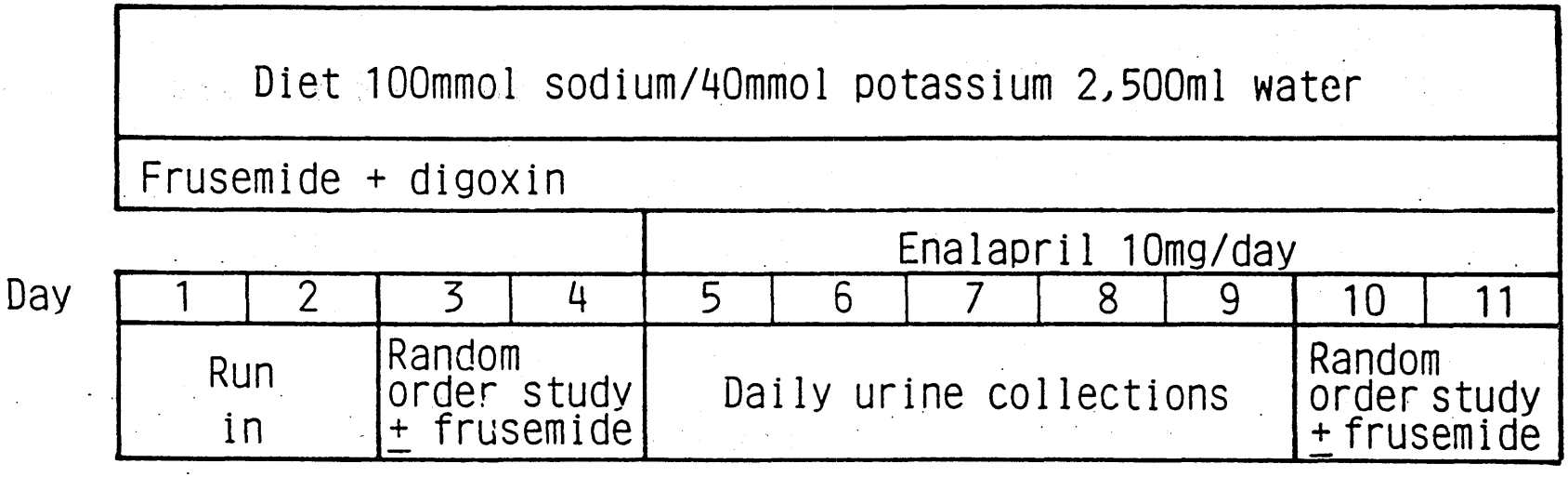


Figure 16.1 Diagrammatic outline of the study design. Patients were placed on a fixed sodium, potassium and water intake throughout the study. The effects of giving or withholding frusemide were studied in random order before and after enalapril.

All studies were performed in the afternoon, after a light lunch, and commenced at midday. Patients were allocated in random order to receive frusemide (given at midday) in the usual oral dose or have it withheld till after the 6-hour study period (and then given at 6 pm). Plasma volumes were measured on the 5th day before administration of enalapril or frusemide. Patients then received 10 mg enalapril per day thereafter at 9 am with their usual dose of frusemide. On days 10 and 11, patients were again allocated in random order to receive or have withheld their usual daily dose of frusemide, while enalapril was continued. Plasma volume measurement was repeated on day 12, before the diet, and was terminated after giving enalapril only.

METHODS

Systemic Haemodynamics

Measurements were taken 2 hours after the study period commenced, shortly after blood samples were taken for the effective renal plasma flow.

Heart rate was measured from the apex beat, and blood pressure using a Hawksley random zero sphygmomanometer. Mean arterial pressure was calculated as diastolic blood pressure +1/3 pulse pressure. Cardiac output was measured using continuous-wave Doppler echocardiography, recordings being taken from the cardiac apex. The outflow tract radius was taken as the aortic valve orifice according to the method of Ihlen et al (see Methods). Total vascular resist-

ance was calculated using the formula: 80 (mean arterial pressure mm Hg) cardiac output ($1min^{-1}$).

Urine Collections

Urine volumes were measured over 6 hours on each of the study days, starting at midday. Samples were taken for the estimation of urinary sodium and potassium. Urinary sodium, potassium and volume were also measured every 24 hours. Patients were weighed daily.

Plasma Volume

Plasma volume was estimated by measuring radioactivity before and 10 minutes after the injection of ^{125}I-human serum albumin. Blood volume was calculated during non- diuretic and diuretic days using the haematocrit, assuming that red cell mass had not changed in the 48- hour study period.

Biochemistry

Blood was taken for electrolytes, urea and creatinine, at the start of the urine collection at the time of sampling for the effective renal plasma flow (ie, 105 minutes), and at the end of the urine collection. Blood was taken for estimation of plasma renin concentration and plasma levels of angiotensin II, aldosterone, noradrenaline and anti-diuretic hormone at 105 minutes only on each study day.

STATISTICAL ANALYSIS

All values are expressed as mean and standard deviation unless otherwise stated. Data not following a normal distribution is expressed as mean, median and range. Differences between treatments were first analysed using analysis of variance. Only if this showed a difference was further analysis carried out using Student's t-test. A Bonferroni correction was used to adjust for the use of multiple t-tests.

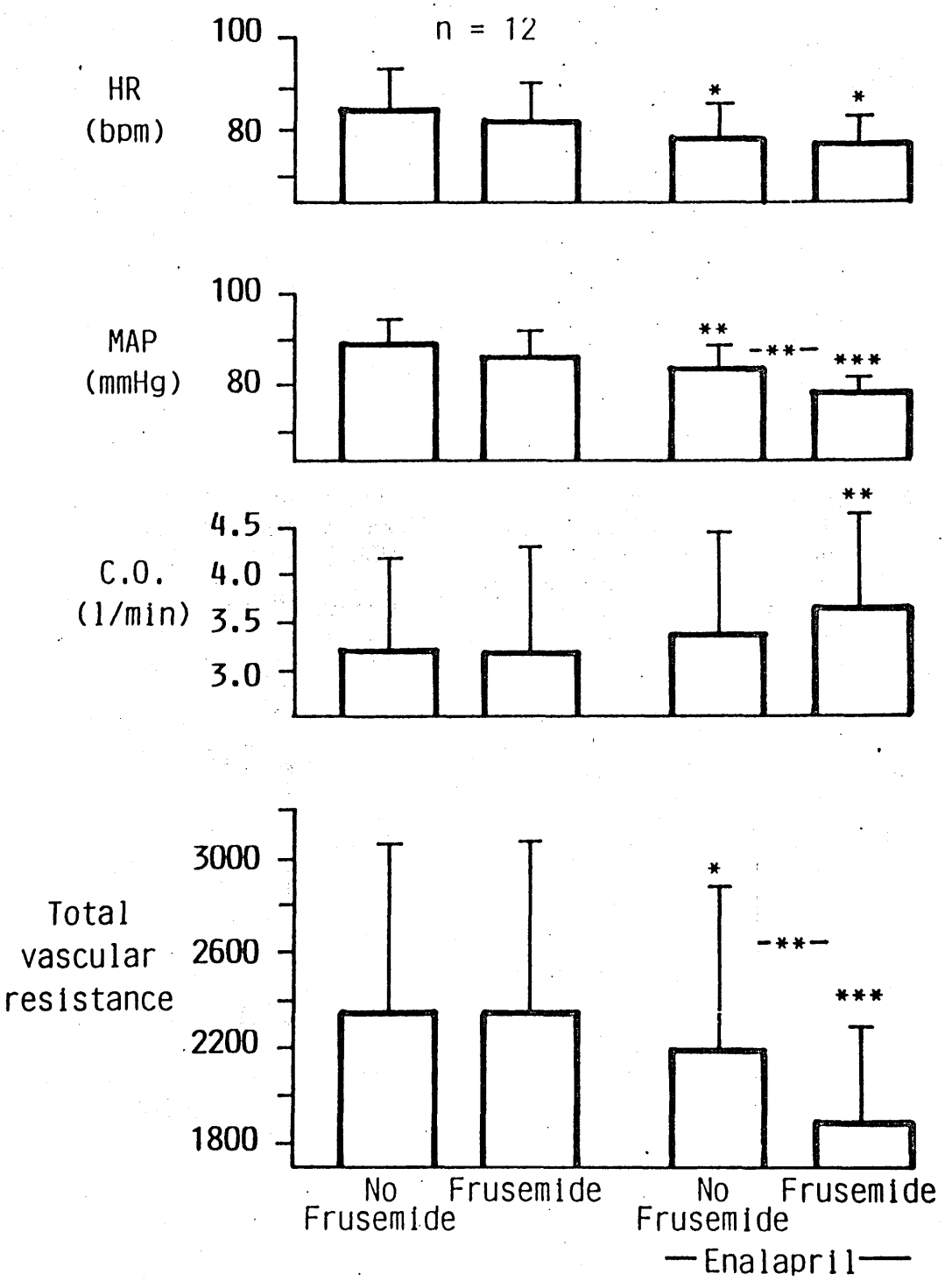
RESULTS

The results are summarised in Figures 16.2-16.6, and Table 16.1.

Systemic Haemodynamics (Figure 16.2)

Heart rate, mean blood pressure, cardiac output and total vascular resistance were unchanged after oral frusemide. After one week, enalapril in the absence of concomitant frusemide therapy significantly reduced the blood pressure, total vascular resistance and heart rate but did not produce a significant increase in cardiac output. The addition of frusemide to enalapril resulted in a further reduction in blood pressure and total vascular resistance, but heart rate was again reduced compared to pre-enalapril values. Cardiac output increased significantly on the combination.

Figure 16.2 Comparison of the effects of frusemide, enalapril and their combination on heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), and total vascular resistance. Figures are mean ±standard deviation. An * over the error bar indicates an effect of enalapril, but between error bars signifies an effect of frusemide. *p<0.05;**p<0.02;***p<0.001.



Renal Haemodynamics (Figure 16.3)

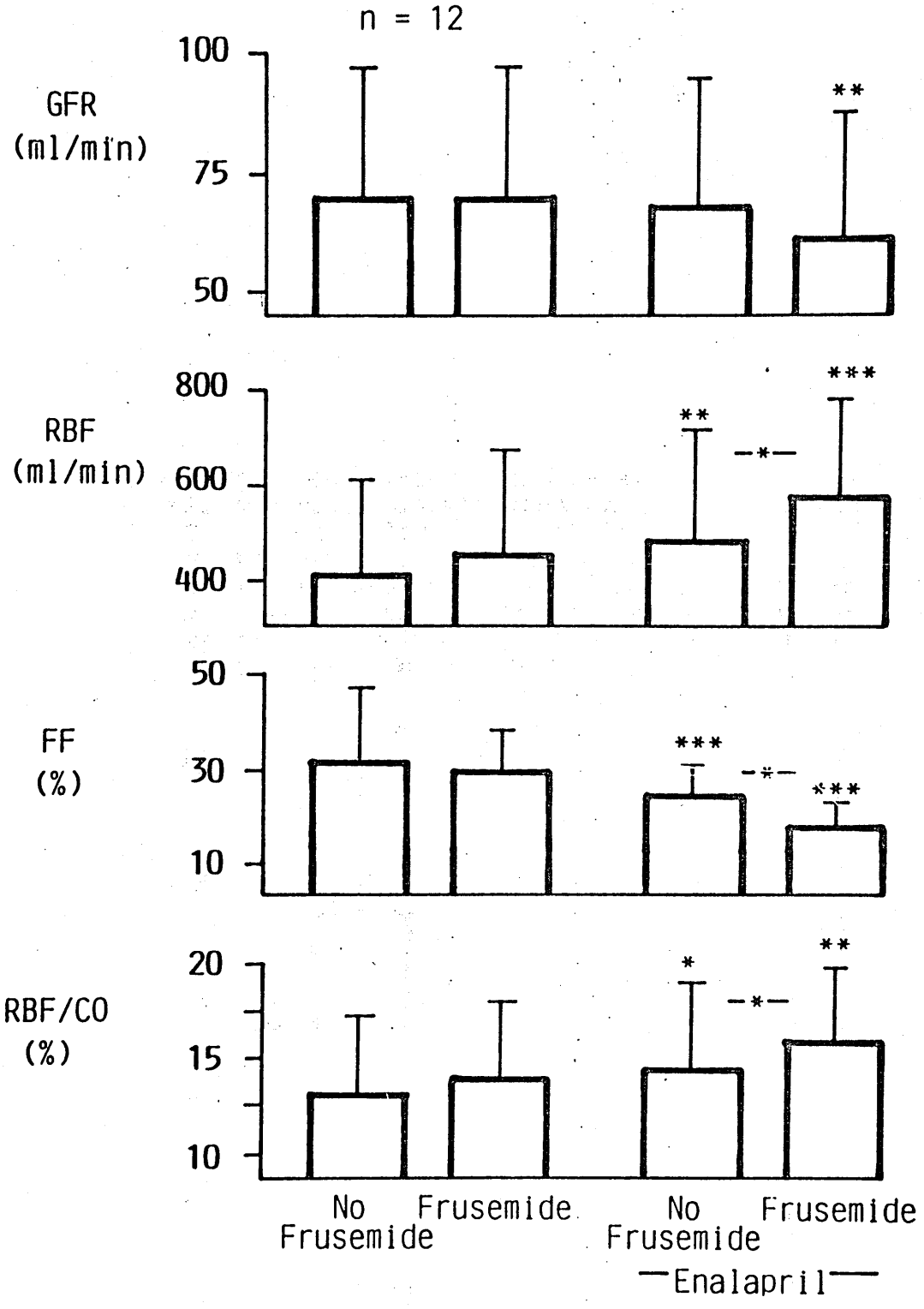
The glomerular filtration rate was unaffected by frusemide alone, while increases in renal blood flow and the percentage of cardiac output to the kidney and the fall in filtration fraction did not achieve statistical significance. Renal vascular resistance was also unaffected.

After enalapril alone, renal blood flow increased significantly without a decline in glomerular filtration rate; consequently, the filtration fraction fell. Renal vascular resistance fell markedly and the proportion of cardiac output distributed to the kidney showed a non-significant increase. The addition of frusemide to enalapril resulted in a further rise in renal blood flow and percentage distribution of cardiac output to the kidney and a further fall in renal vascular resistance and filtration fraction. However, glomerular filtration rate also fell.

Plasma Volume and Haematocrit (Figure 16.4)

Plasma volume increased by approximately 10% after one week of enalapril, while haematocrit fell. The decrease in blood volume after frusemide did not achieve statistical significance either before or after therapy with enalapril.

Figure 16.3 Comparison of the effects of frusemide, enalapril and their combination on glomerular filtration rate (GFR), renal blood flow (RBF), filtration fraction (FF) and the percentage of the cardiac output delivered to the kidneys (RBF/CO). Figures are mean ±standard deviation. An * over the error bar indicates an effect of enalapril, but betwen error bars indicates signifies an effect of frusemide. *p<0.05; **p<0.01; ***p<0.001.



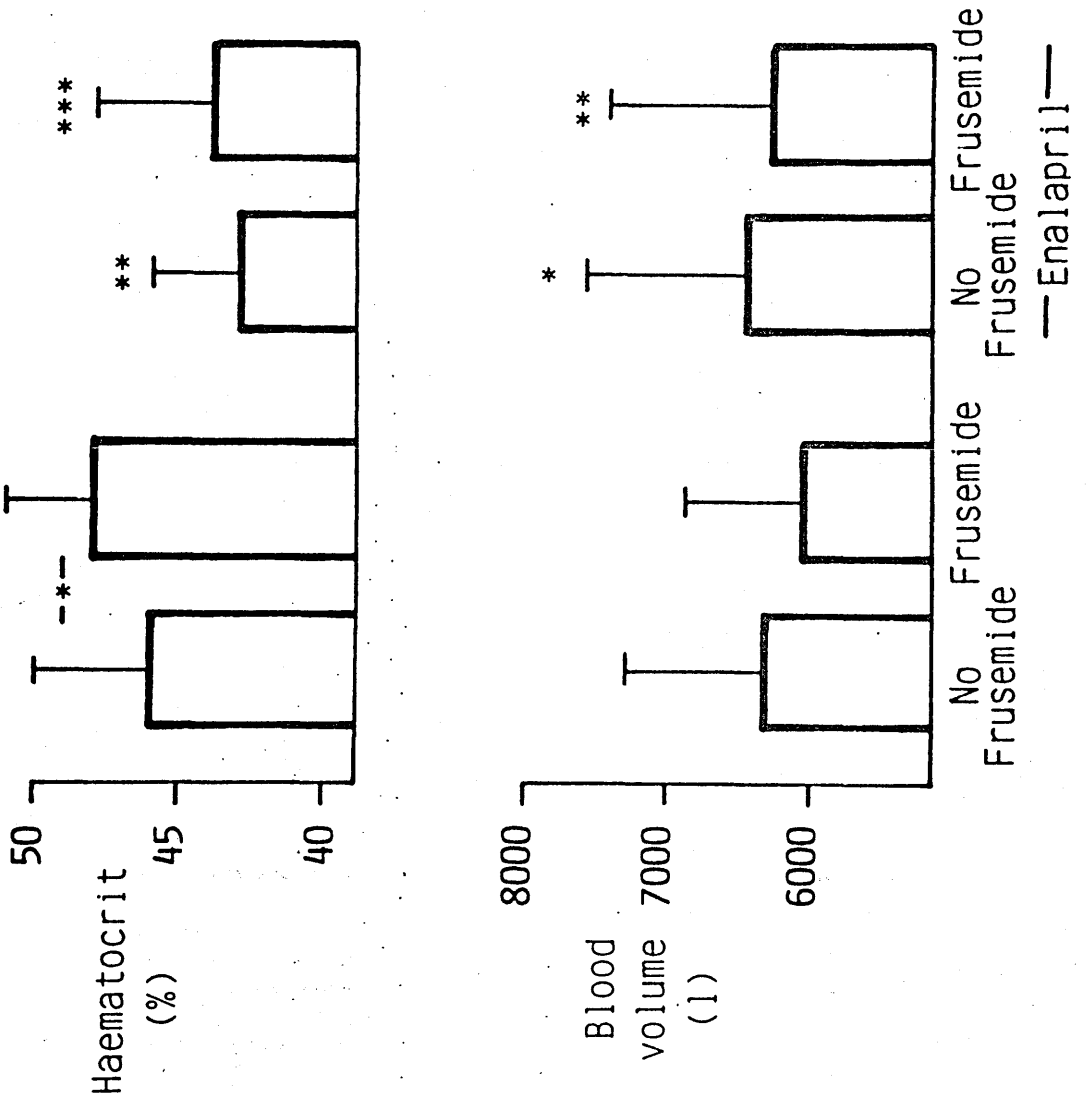


Figure 16.4 Comparison of the effects of frusemide, enalapril and their combination on haematocrit and blood volume. Figures are mean ±standard deviation. An * over the error bar indicates an effect of enalapril, but between error bars signifies an effect of frusemide. *p<0.05;**p<0.02;***p<0.001.

Neuroendocrine Effects **(Table 16.1)**

Plasma concentrations of active renin, angiotensin II, aldosterone, anti-diuretic hormone and noradrenaline were all elevated in the absence of either frusemide or enalapril. Oral frusemide increased levels of each hormone.

Enalapril alone resulted in a significant reduction in plasma concentrations of angiotensin II, aldosterone, anti-diuretic hormone and noradrenaline, with a concomitant increase in plasma active renin concentrations. No increase in plasma concentrations of angiotensin II, aldosterone and noradrenaline were observed after frusemide. However, the increase in plasma active renin concentration and anti-diuretic hormone after frusemide were not inhibited by enalapril.

Serum Biochemistry **(Figure 16.5)**

Serum urea, creatinine, osmolality and sodium were unaffected by the acute administration of a further dose of frusemide. However, serum potassium fell acutely in response to frusemide.

After one week of enalapril, serum sodium and osmolality had fallen, while upward trends in serum potassium, urea, and creatinine were non-significant. Administration of frusemide with enalapril resulted in no significant changes in serum biochemistry.

Table 1 Comparison of the effects of frusemide, enalapril and their combination on plasma concentrations of active renin concentration (PARC), angiotensin II (P.Ang II), aldosterone (P.Aldo), noradrenaline (NA) and anti-diuretic hormone (ADH)

	No frusemide		Frusemide alone	Enalapril alone		Enalapril + frusemide
PARC (μU ml^{-1})						
Mean	245		343	1822‡		2434‡
Median	82	$P<0.01$	165	1050	$P<0.001$	2796
Range	3–828		5–1210	11–6160		55–7056
P.Ang.II (pmol l^{-1})						
Mean	103		136	10‡		20‡
Median	47	$P<0.01$	84	9	NS	19
Range	5–392		11–398	2–22		2–28
P.Aldo (nmol l^{-1})						
Mean	677		849	225‡		220‡
Median	466	$P<0.01$	520	187	NS	226
Range	262–1876		337–3326	90–392		100–392
P.NA (nmol l^{-1})						
Mean	6·7		9·5	4·1†		4·7‡
Median	4·7	$P<0.01$	7·1	3·0	NS	3·9
Range	1·9–25·0		2·5–39·1	1·2–13·3		1·4–13·5
ADH (pg ml^{-1})						
Mean	3·3		5·0	1·9†		3·8 NS
Median	3·3	$P<0.01$	6·3	1·9	$P<0.01$	5·0
Range	0·5–6·7		0·6–12·3	0·2–3·2		0·7–7·3

P values indicate a significant effect of frusemide.
†,‡An effect of enalapril: +, $P<0.01$; ‡, $P<0.001$.

Table 16.1 Comparison of the effects of frusemide, enalaparil and their combination on plasma concentrations of active renin concentration (PARC), angiotensin II (P. Ang II), aldosterone (P.Aldo), noradrenaline (NA) and anti-diuretic hormone (ADH).

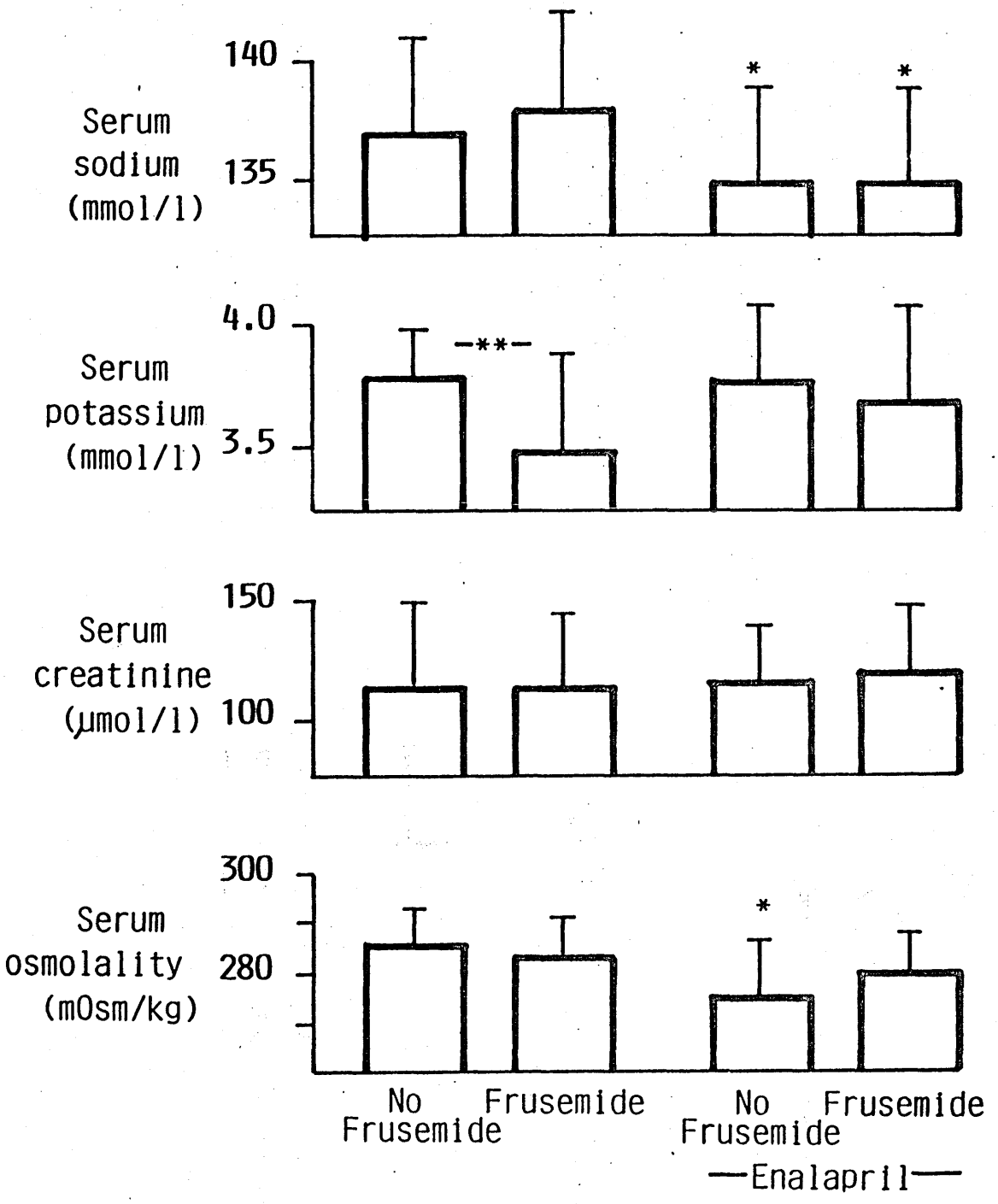


Figure 16.5 Comparison of the effects of frusemide, enalapril, and their combination on serum biochemistry. Figures are mean±standard deviation. An* over the error bar indicates an effect of enalapril, but between error bars signfies an effect of frusemide. *$p<0.05$;**$p<0.01$.

Urine Biochemistry (Figure 16.6)

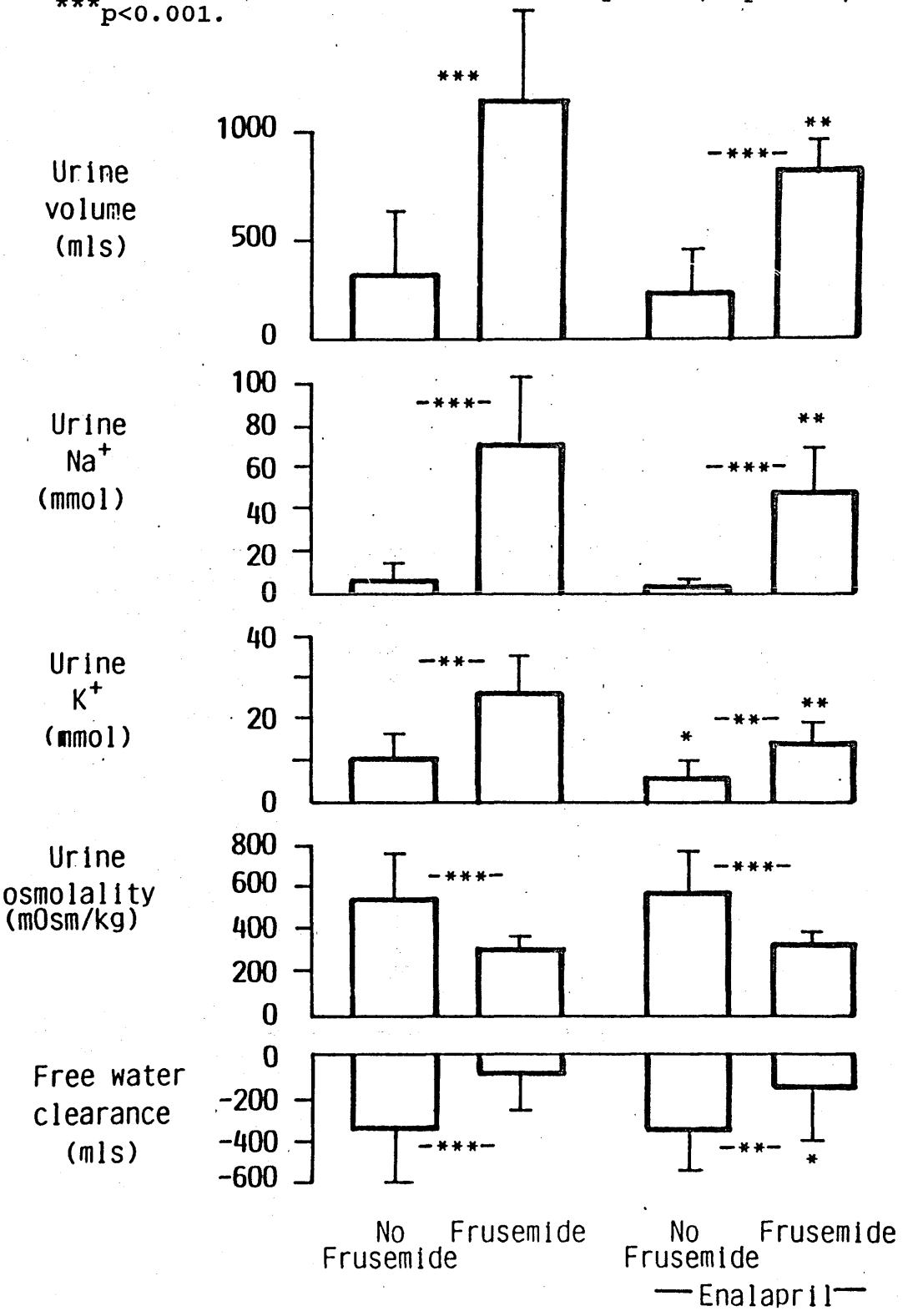
In the absence of a diuretic, renal sodium and potassium excretion was low. With the administration of frusemide, urinary sodium and potassium content and concentration and the fractional excretion of these electrolytes filtered at the glomerulus increased. Urine volume and free water clearance increased while urine osmolality fell.

With enalapril alone, urine sodium content and concentration were unchanged, but urinary losses of potassium were reduced. With the administration of frusemide, the urinary content and concentration of sodium and potassium, urine volume and free water clearance were all reduced when compared to the effects of frusemide in the absence of enalapril.

Changes over the first week

Over the first week, 123+156 mmol sodium and 107+98 mmol potassium was retained, and weight increased by 2.3+2.1 kg. Three patients developed oedema (weight gain 3.2, 4.2 and 6.1 kg) over the first week.

Figure 16.6 Comparison of the effects of frusemide, enalapril and their combination on urine volume and biochemistry (Na, sodium;K, potassium). Figures are mean±standard deviation. An * over the error bar indicates an effect of enalapril, but between error bars signifies an effect of frusemide. *p<0.05;**p<0.01; ***p<0.001.



CHAPTER 17:THE EFFECTS OF CAPTOPRIL ON SERUM DIGOXIN AND URINARY UREA AND DIGOXIN CLEARANCES IN PATIENTS WITH CONGESTIVE HEART FAILURE

Since digoxin is largely excreted by the kidney unchanged, glomerular filtration rate is important in regulating the serum level of digoxin. Although the value of digoxin in patients with heart failure is still controversial, it is still commonly used and is standard therapy for those patients with atrial fibrillation, a common arrhythmia in this setting.

Angiotensin-converting enzyme inhibitors are now being prescribed frequently in patients with heart failure. While captopril increases renal blood flow in patients with congestive heart failure by preventing angiotensin II-mediated renal artery constriction, it reduces glomerular filtration rate. The latter might be predicted, as angiotensin II preferentially constricts efferent arterioles, thus maintaining glomerular hydrostatic pressure and glomerular filtration rate in the face of falling renal perfusion pressure.

Patients with congestive heart failure are prone to sudden death, presumably from arrhythmias, and these could be increased by the effects of digoxin. However, captopril has many other effects, including the correction of hypokalaemia, which might ameliorate the toxic effects of

digoxin excess. We have previously demonstrated in double-blind studies that captopril can increase serum digoxin. The present study was undertaken to further characterise the mechanisms underlying this effect.

PATIENTS

Twelve patients (mean age 59±9 years), 10 men and 2 women with NYHA Class III or IV heart failure were studied. Eight had ischaemic heart disease and 4 had congestive cardiomyopathy. All were receiving digoxin (mean dose 0.21±0.01 mg/day) for more than 3 months, together with frusemide (mean dose 127±49 mg/day). No patient had angina, significant respiratory disease, or serum creatinine above 200 mol/l. All gave written consent to the trial, which was approved by the hospital's Ethical Supervisory Committee. Creatinine and digoxin clearance were estimated before and after captopril therapy (duration 3-8 weeks: mean 4 weeks).

METHODS

Creatinine and digoxin clearance were calculated from 6-hour urine collections, and venous samples were taken at 0, 3 and 6 hours. These studies were peformed 6 hours after the last dose of digoxin. Fractional urinary excretion of urea and digoxin was calculated from the amount excreted in the urine, divided by the amount filtered at the glomerulus (that is, serum concentration x creatinine clearance) over the 6 hours of study.

Digoxin was measured using fluorescence polarisation immunoassay, urine being diluted 1:10 with "blank" (non-digoxin-containing) serum. This assay is specific for digoxin and its cardioactive metabolites, digoxigenin and the mono- and bis-digitoxoside.

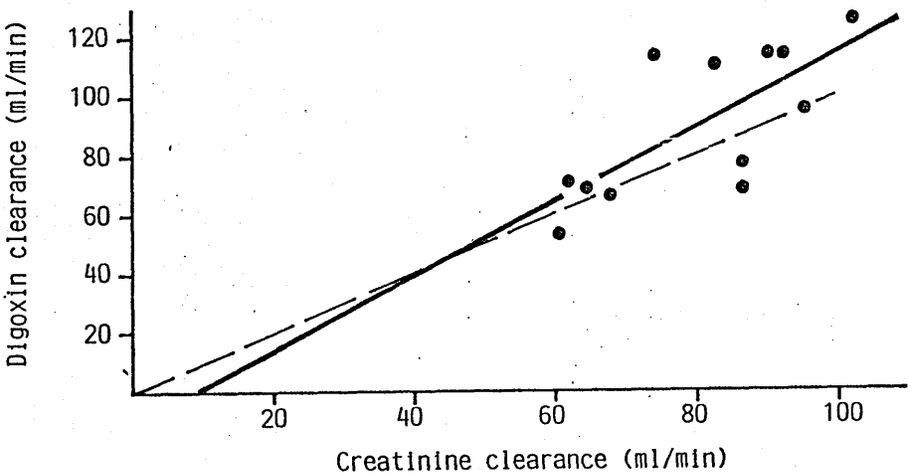
RESULTS

Before captopril, urea and creatinine clearance were correlated ($r=0.67;p<0.02$), as were urea and digoxin clearance ($r=0.80;p<0.002$) and creatinine and digoxin clearance ($r=0.72;p<0.01$). **(Figures 17.1)** Digoxin clearance was slightly greater than creatinine clearance, while both were greater than urea clearance. With captopril, urinary creatinine and digoxin clearance fell and a small rise in serum digoxin occurred. However, the fall in digoxin clearance was significantly greater than the fall in creatinine clearance ($p<0.05$). **(Figure 17.1)** Fractional urinary excretion of urea and digoxin declined on captopril suggesting that increased tubular reabsorption or reduced tubular secretion had taken place. **(Table 17.1)**

TABLE 17.1

EFFECTS OF CAPTOPRIL ON URINARY DIGOXIN CLEARANCE

		BASELINE		CAPTOPRIL
SERUM DIGOXIN	(mmol/L)	1.5(0.5)	p<0.05	1.7(0.5)
URINARY DIGOXIN	(ug)	41(11)	ns	44(16)
CREATININE CLEARANCE	(ml/min)	81(14)	p<0.02	72(19)
UREA CLEARANCE	(ml/min)	37(13)	p<0.01	29(11)
DIGOXIN CLEARANCE	(ml/min)	89(25)	p<0.01	69(22)
FRACTIONAL EXCRETION OF				
- UREA	(%)	111(22)	p<0.05	96(18)
- DIGOXIN	(%)	46(14)	p<0.05	40(9)



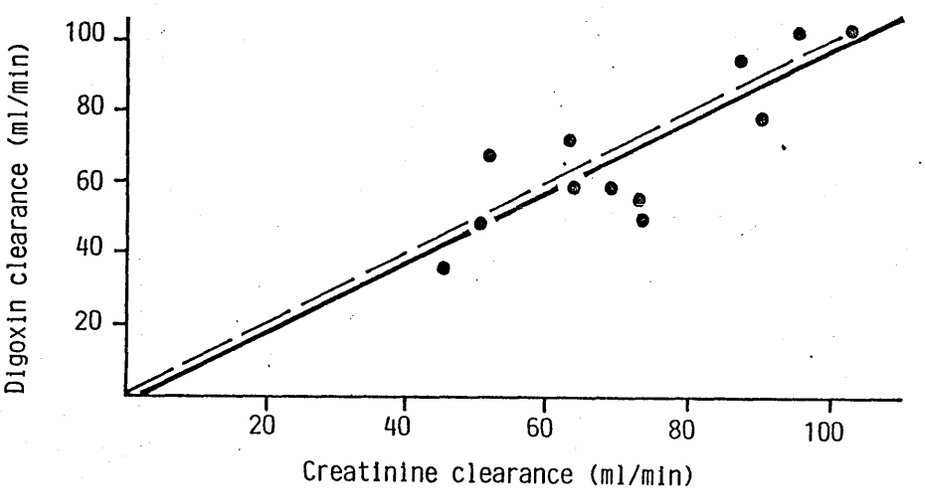


Figure 17.1 Correlation of creatinine clearance and digoxin clearance before (top panel) treatment with captopril ($r=0.72; p<0.01$). Correlation of creatinine clearance and digoxin clearance after (lower panel) treatment with captopril ($r=0.84; p<0.002$).

Solid line is line of correlation and broken line is the line of identity.

CHAPTER 18: THE EFFECTS OF SHORT-TERM CONVERTING-ENZYME INHIBITION ON RENAL TUBULAR FUNCTION AND ATRIAL NATRIURETIC PEPTIDE

INTRODUCTION

Previous studies have reported that the introduction of captopril or enalapril is associated with weight gain due to fluid retention. This is self-limiting in most instances and is reversed by longer-term therapy. (See Chapters 15,16 & 17)

These findings are contrary to prior empirical thoughts on the subject. It was believed that improved renal blood flow and reduced angiotensin II, aldosterone and sympathetic activity would lead to a diuresis. However, a fall in glomerular filtration, arterial and atrial pressure could outweigh these influences.

The present study investigated the effects of enalapril on renal haemodynamics and tubular function.

PATIENTS

Written, informed consent was obtained from 20 patients (mean age 59$\pm$7 years) with heart failure due primarily to left ventricular dysfunction. Four patients were women. The aetiology was ischaemic heart disease in 12 patients and idiopathic dilated (congestive) cardiomyopathy in 8. All patients had received digoxin and diuretics for at least 3

months prior to investigation. The median dose of digoxin was 0.25 mg day^{-1} (range 0.125-0.375 mg day^{-1}), and of frusemide 120 mg day^{-1} (range 80-240 mg day^{-1}). Fourteen patients were in New York Heart Association Class III and 6 in Class IV. Fifteen patients were in sinus rhythm.

All patients were commenced on a diet with a content of 100 mmol sodium, 40 mmol potassium diet, and 2,500 ml total fluid intake for 48 hours prior to the study and for the 9 days of the study. In order to achieve accurate dietary balance the patient was required to eat an identical diet each day for the duration of the study.

STUDY DESIGN

Patients were admitted to the ward and commenced on the above diet 48 hours before the study. Renal function was then studied in the presence of absence of a diuretic on separate days (days 3 & 4). Patients were then commenced on enalapril, and studies repeated in the presence or absence of a diuretic on days 10 & 11.

All studies were performed in the afternoon, after a light lunch and commenced at midday. Patients were allocated in random order to receive frusemide (given at midday) in the usual oral dose, or have it withheld till after the 6-hour study period (and then given at 6 pm). Patients then received 10 mg enalapril per day thereafter at 9 am with their usual dose of frusemide. On days 10 and 11, patients

were again allocated in random order to receive or have withheld their usual daily dose of frusemide while enalapril was continued.

METHODS

Urine Collections

Urine volumes were measured over 6 hours on each of the study days, starting at midday. Samples were taken for the estimation of urinary sodium, potassium, magnesium, and phosphate. Urinary sodium, potassium and volume were also measured every 24 hours. Patients were weighed daily.

Biochemistry

Blood was taken for electrolytes, urea and creatinine at the start of the urine collection, at the mid-point, and at the end of the urine collection.

Atrial Natriuretic Peptide

Plasma atrial natriuretic peptide was measured before, 24 hours after the administration of enalapril, and at the end of the study.

STATISTICAL ANALYSIS

All values are expressed as mean and standard deviation unless otherwise stated. Data not following a normal distribution is expressed as mean, median and range. Differences between treatments were first analysed using

analysis of variance. Only if this showed a difference was further analysis carried out using Student's t-test. A Bonferroni correction was used to adjust for the use of multiple t-tests.

RESULTS

Clinical Outcome (Figure 18.1)

Weight increased by 1.7 kg over the first week, with a maximum around the fifth day after starting enalapril. Four patients subsequently required an increase in diuretic dose after the study in view of the development of new or worsening oedema.

The lowest measured blood pressure was on the second day after commencing enalapril. Blood pressure rose thereafter.

Atrial Natriuretic Peptide (Figure 18.1)

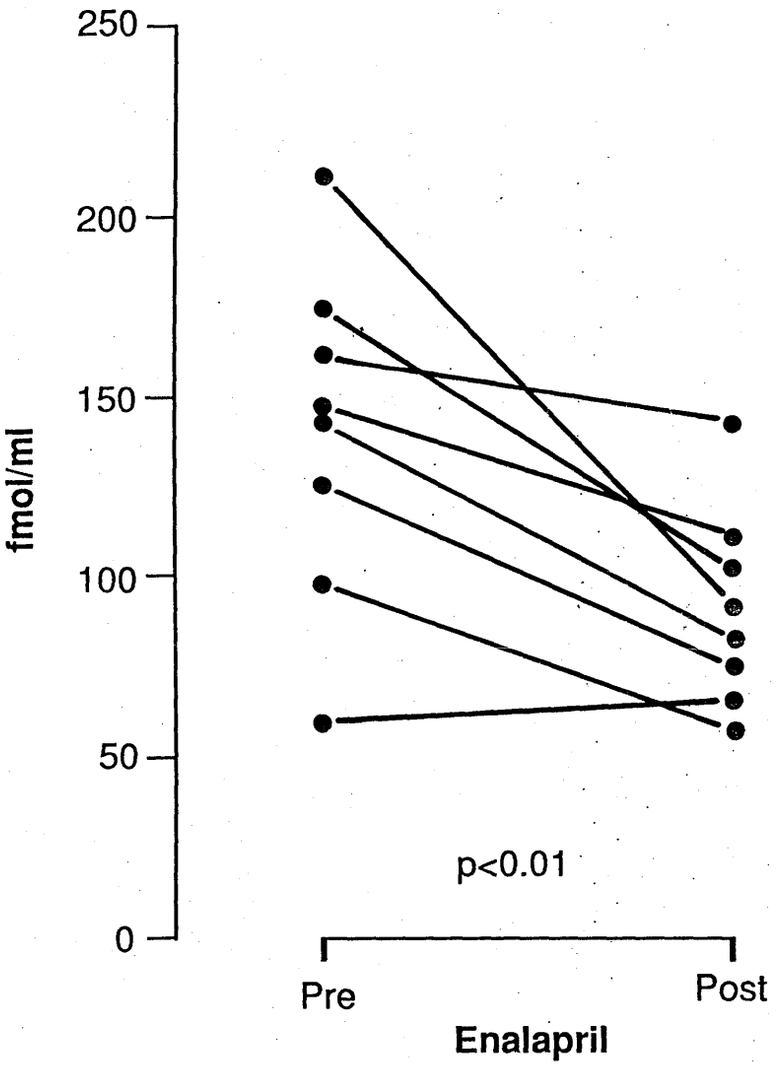
Plasma levels of atrial natriuretic peptide fell markedly 24 hours after the administration of enalapril. Levels tended to rise over the duration of the study, accompanied by weight gain.

Serum Biochemistry (Table 18.1)

Serum sodium fell over the study period, while other electrolytes, urea, and creatinine were unchanged.

Creatinine Clearance (Table 18.2)

FIGURE 18.1



Plasma levels of atrial natriuretic peptide before and after 24 hours of ACE inhibition with enalapril

TABLE 18.1

		NO DIURETIC	DIURETIC	ACE	ACE+ DIURETIC
PLASMA CONCENTRATION					
SODIUM	(mmol/L)	136(2)	137(2)	135(2)	*135(3)
POTASSIUM	(mmol/L)	3.8(0.2)	3.7(0.3)	3.8(0.2)	3.7(0.3)
UREA	(mmol/L)	8.9(2.1)	8.1(1.6)	8.7(1.8)	9.0(1.8)
CREATININE	(umol/L)	112(12)	113(14)	116(18)	116(21)
PHOSPHATE	(mmol/L)	1.2(0.2)	1.1(0.2)	1.1(0.2)	1.2(0.2)
MAGNESIUM	(mmol/L)	0.81(0.06)	0.78(0.04)	0.82(0.04)	**0.83(0.04)
OSMOLALITY	(mOsm/L)	284(4)	284(6)	*279(6)	**279(4)

For comparisons before and after enalapril with and without diuretic
* = $p<0.05$ ** = $p<0.02$
no symbol = not significant.

TABLE 18.2
EFFECTS OF SHORT-TERM ENALAPRIL ON URINE COMPOSITION

		NO DIURETIC	DIURETIC	ACE	ACE+ DIURETIC
URINE VOLUME	(mls)	251(50)	1040(140)	221(32)	**836(130)
CONCENTRATION					
SODIUM	(mmol/L)	16(8)	72(12)	**11(4)	67(19)
POTASSIUM	(mmol/L)	49(14)	29(6)	***30(10)	***16(2)
UREA	(mmol/L)	325(64)	97(18)	322(80)	102(22)
CREATININE	(umol/L)	12.3(3.4)	2.8(0.4)	12.7(2.8)	3.2(0.3)
PHOSPHATE	(mmol/L)	29(8)	6(1)	*22(2)	**4(1)
MAGNESIUM	(mmol/L)	3.1(0.9)	1.7(0.3)	**1.9(0.6)	**1.1(0.2)
OSMOLALITY	(mOsm/L)	552(100)	315(24)	508(104)	320(40)
CREAT CL	(mls/min)	73(14)	73(11)	67(12)	*66(11)
UREA CL	(mls/min)	28(8)	40(12)	24(8)	*27(6)
UNaV	(mmols)	3.8(1.6)	77.5(17.6)	*2.2(0.6)	**55.1(11.8)
UKV	(mmols)	11.3(3.2)	28.7(4.2)	**6.4(2.0)	****12.9(2.6)
UPO4V	(mmols)	7.1(1.8)	6.2(0.8)	**4.5(0.8)	****3.3(1.0)
UMgV	(mmols)	0.7(0.2)	1.7(0.2)	*0.4(0.2)	****0.9(0.2)
FENa	(%)	0.12(0.04)	2.45(0.42)	**0.08(0.02)	1.93(0.66)
FEK	(%)	15(10)	38(20)	*8(4)	**17(6)
FEUrea	(%)	38(6)	53(12)	34(8)	43(8)
FEPO4	(%)	26(8)	24(6)	*20(4)	****13(4)
FEMg	(%)	3.8(1.2)	9.3(2.4)	*2.2(0.6)	**5.1(1.4)
Na/PO4	.	0.6(0.2)	12.7(2.6)	0.5(0.2)	*18.3(3.8)
Na/Mg	.	5.1(1.0)	46.8(11.6)	6.3(1.9)	*66.3(17.8)
Na/K	.	0.4(0.2)	2.8(0.8)	0.4(0.2)	**4.3(0.6)

For comparisons before and after enalapril with and without diuretic
* = p<0.05 ** = p<0.02 *** = p<0.01 **** = p<0.001
no symbol = not significant.

All comparisons between the periods with and without diuretic were significant at p<0.001 apart from the following:-
not significant: creatinine clearance, UPO4V, FEPO4.
p<0.05 : potassium and magnesium concentration
urea clearance and FE Urea.

FE = FRACTIONAL EXCRETION Na = sodium. K = potassium
PO4 = phosphate. Mg = magnesium. CL = clearance.

This was lower after one week's treatment with enalapril, but the change was only significant for the combination of enalapril and diuretic.

Urine Volume (Table 18.2)

Urine volume increased after frusemide, as expected. After treatment with enalapril, urine volumes were reduced, but the change was again only significant when compared to baseline on the combination of frusemide and enalapril.

Urine Biochemistry (Table 18.2)

Urinary sodium, potassium and magnesium excretion were all increased by frusemide but phosphate was not. Urinary sodium, potassium, magnesium and phosphate excretion were all reduced by enalapril. This occurred both in the presence of and absence of frusemide. The fractional excretion of each of these electrolytes was also reduced by enalapril, suggesting increased tubular reabsorption. The ratio of sodium to phosphate increased on the combination of frusemide and enalapril compared to frusemide alone, suggesting increased proximal tubular reabsorption of sodium.

Over the 5 days between the 2 study periods, despite a constant sodium, potassium and fluid intake, weight increased (see above). A net positive balance of 187 $\pm$133 mmol sodium and 76$\pm$60 mmol potassium occurred.

CHAPTER 19: THE EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH ANGINA PECTORIS

INTRODUCTION

Patients suffering from angina pectoris and heart failure are difficult to manage and have a poor prognosis. In carefully selected patients, re-vascularisation may be of benefit but, due to poor ventricular function, age, and other associated problems, the operative morbidity and mortality is high.[711] Moreover, it is controversial whether successful re-vascularisation can improve severely depressed left ventricular function.[712-714]

Medical therapy of angina and heart failure might include efforts to reduce pre- and afterload on the left ventricle, coronary vasodilatation, and limitation of heart rate response to exercise. Reduction in myocardial contractility is likely to be detrimental. Most calcium antagonists and beta-adrenergic receptor antagonists depress cardiac function and are contra- indicated in heart failure.[715,716] There is some controversial evidence that beta-adrenergic receptor antagonists may be of benefit in heart failure, but studies demonstrating success have started with long periods of dosing which would be sub-therapeutic for angina.[717-719] Angiotensin converting enzyme (ACE) inhibitors exhibit several desirable properties resulting in venous and arterial dilatation and coronary vasodilatation, which theoretically should be of benefit in angina and heart

failure.[720-721] Some studies have shown that ACE inhibitors may reduce exercise-induced myocardial ischaemia in patients with angina,[722,727] though others have been unable to confirm this.[728,730] These studies have concentrated on patients with angina but without evidence of heart failure. It might be expected that patients with the combination of heart failure and angina would have more to gain in view of their often markedly elevated preload and afterload which is in a large part due to activation of the sympathetic nervous and renin-angiotensin systems.

Studies on animals have also suggested that ACE inhibitors, particularly captopril, reduce myocardial damage and arrhythmias during prolonged ischaemia and reperfusion.[731-737]

A double-blind placebo cross-over controlled trial of captopril compared to placebo in patients with heart failure and angina pectoris is reported here.

PATIENTS

We studied 14 men and 4 women who had heart failure, coronary artery disease and symptoms consistent with angina pectoris. The mean age was 63 $\pm$6 years.

All 18 had a history of one or more myocardial infarctions confirmed by enzyme and electrocardiographic changes and had symptoms consistent with Canadian Heart Association Class III. No patient had had a myocardial infarction

within 3 months of the study. The median number of infarcts per patient was 2 (range 1-4). Three had anterior Q waves, indicative of infarction, 3 inferior and posterior changes, and 5 both inferior and anterior Q waves. Seven patients had left bundle branch block. Coronary artery disease was further confirmed by angiography in 14 patients. All patients were in sinus rhythm. Heart failure was confirmed by physical examination, the presence of radionuclide ventriculography and haemodynamic criteria. The left ventricular end-diastolic pressure was 23 $\pm$8 mm Hg in the 14 patients who were catheterised. The median dose of frusemide was 120 mg/day (range: 40 - 240 mg/day), 10 were receiving digoxin (median dose: 0.25mg/day), 4 nitrates, 2 nifedipine and 2 the combination of the above.

The presence of reversible myocardial ischaemia was based on a history of typical angina pectoris, with pain consistently induced by exercise and relieved by rest. Pre-existing electrocardiographic (ECG) abnormalities and treatment with digoxin rendered accurate interpretation of exercise-induced ECG changes impossible.

METHODS

Symptoms of breathlessness, fatigue and angina pectoris were assessed by visual analogue scores, and use of sublingual glyceryl trinitrate was recorded in a diary. Patients were also asked to state their preferred treatment in this double-blind trial.

Heart rate was counted from the radial pulse and blood pressure determined using a Hawksley random-zero sphygmomanometer. Weight and venous pressure were measured and the presence of a third heart sound sought.

Venous blood was taken after 30 minutes of supine rest, and serum plasma concentrations of electrolytes, renin, angiotensin II and noradrenaline were measured.

Exercise capacity was determined using two special treadmill protocols. A "FAST" protocol was used in an attempt to induce maximal cardio-respiratory stress in the patient, and a "SLOW" protocol to more nearly simulate patient's everyday activity where patients are more likely to be limited by "peripheral" factors. Respiratory gas analysis was carried out using an Horizon Mobile Metabolic Cart (Sensormedics) to determine maximal oxygen consumption.

Rest and exercise left ventricular ejection fractions were determined by multiple uptake gated acquisition and a multi-crystal gamma camera during supine bicycle exercise. Exercise started at 25W and increased by 25W every 2 minutes.

Ventricular arrhythmias were monitored for 48 hours in each phase by ambulatory ECG monitoring.

STUDY DESIGN

After a 2-week run-in period to standardise therapy and familiarise patients with procedures, baseline assessments were carried out. Patients were given a test dose of 6.25 mg of captopril in an open fashion to ensure no severe first-dose adverse reaction. If none occurred, patients were randomised to identical placebo or captopril (25 mg tid) in a double-blind fashion for a 2-week period. If the patient's symptoms remained unchanged and the standing systolic blood pressure was greater than 100 mm Hg, the dose of captopril was increased to 50 mg tid (or identical placebo) for a further 4 weeks. Patients were then reassessed and crossed over double-blind to receive the alternative therapy in an identical manner for a further 6 weeks before final assessment.

STATISTICAL ANALYSIS

Order and period effects were excluded by comparing the differences between observations for the captopril and placebo phases using two-sample t-tests; results for the captopril and placebo phases were compared with Student's T-test with log transformation if appropriate. Where variables (such as exercise) were measured on more than one occasion, the Bonferroni correction was used to adjust for multiple t-tests. The Chi-squared test was applied to test for differences in distribution of discrete variables.

RESULTS

Sixteen patients completed the study, one died suddenly at home. He did not report any increase in angina prior to his death. He was receiving placebo. One patient who was on nifedipine and nitrates developed a low arterial pressure (68/44 mm Hg) on the addition of captopril. Although he did not exhibit features of syncope or pre-syncope, he was withdrawn from the trial due to progressive hyponatraemia, uraemia, oliguria and weight gain. This resolved on stopping nifedipine and his blood pressure rose to 96/72 mm Hg. No other side-effects were noted. Five patients received 50 mg tid captopril and eleven 25 mg tid. Symptomatic responses appeared unrelated to the dose of captopril used.

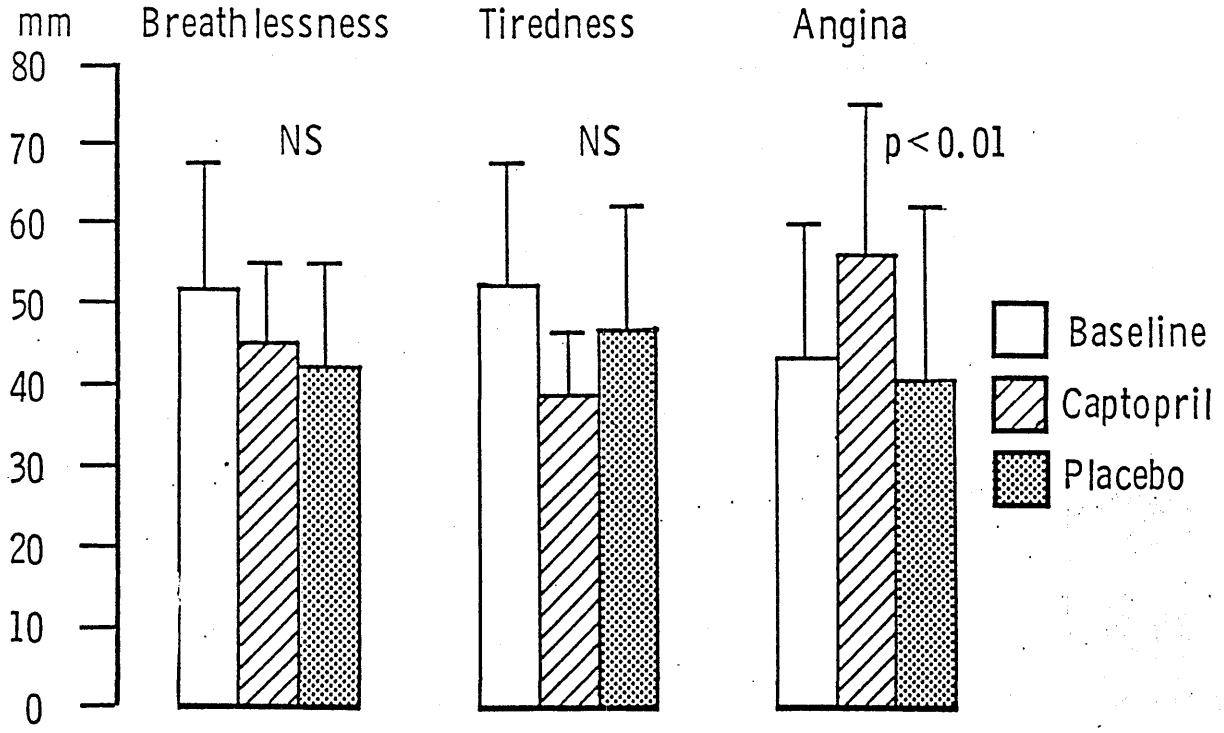
Symptoms (Figures 19.1 & 19.2)

Visual analogue scores for breathlessness and fatigue were unchanged but, compared to placebo, scores for angina were worse on captopril. The consumption of sublingual nitrates was also increased. Nine patients preferred placebo, 4 had no preference but only 3 preferred captopril ($p<0.05$ comparing captopril preference to other outcomes)

Clinical Signs

Resting heart rate and blood pressure were lower on captopril compared to placebo. Body weight was unchanged. Physical signs of heart failure at rest were not markedly changed.

Figure 19.1 **Visual Analogue Scores**



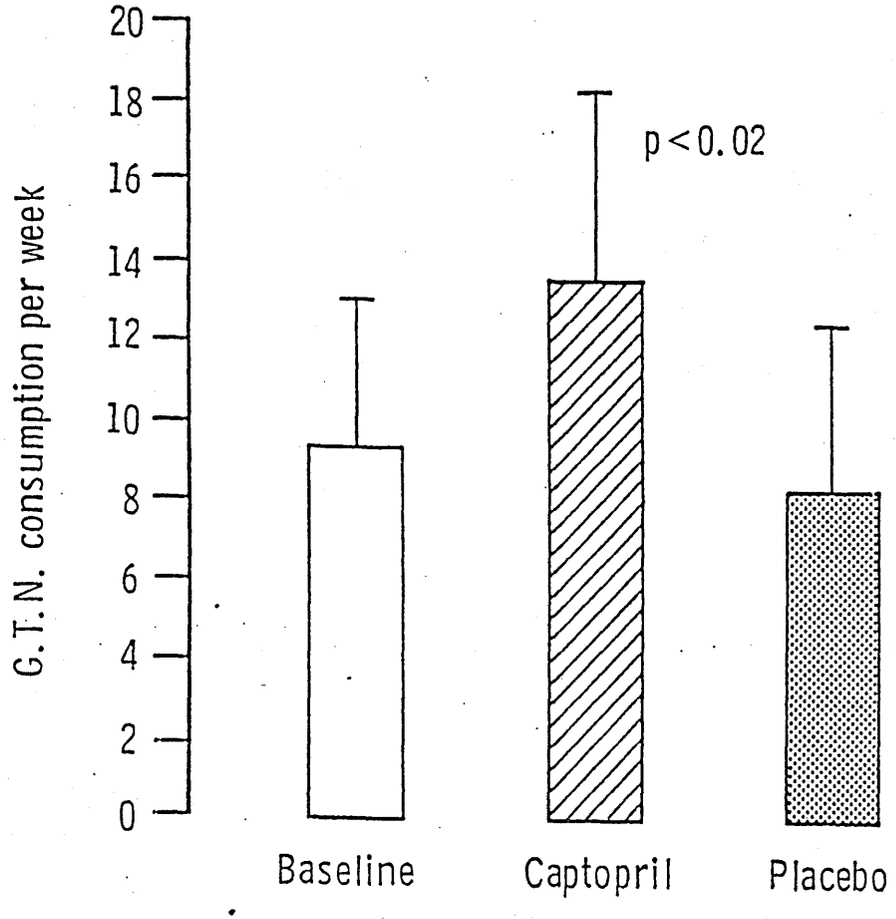

20
18
16
14
12
10
8
6
4
2
0
G.T.N. consumption per week
p < 0.02
Baseline
Captopril
Placebo

Figure 19.2

Biochemistry (Table 19.1)

Plasma potassium, urea and creatinine rose while plasma sodium was unchanged on captopril. Plasma renin concentration and plasma concentrations of angiotensin II and noradrenaline fell.

Treadmill Exercise Testing (Table 19.2)

At baseline, all patients stopped with symptoms of angina and breathlessness during the "FAST" protocol but only 10 out of 18 during the "SLOW" test. Two stopped with breathlessness and 6 with fatigue during the latter protocol.

After statistical correction for multiple exercise tests, exercise duration was unaltered by the "SLOW" protocol but 13 patients became limited by angina compared to 6 during the placebo phase ($p<0.05$). Exercise performance was significantly worse on captopril during the "FAST" protocol and patients always stopped due to breathlessness and angina. Maximum exercise heart rate was higher during the "FAST" compared to the "SLOW" protocol, but was unchanged by the introduction of captopril. Maximum systolic blood pressure was similar during "FAST" and "SLOW" protocols but was consistently lower during therapy with captopril. Recordings of diastolic blood pressure were also lower on captopril but these non-invasive estimates were considered technically unreliable and are not considered further.

TABLE 19.1 TREADMILL EXERCISE TESTING

	BASELINE	CAPTOPRIL	PLACEBO	p<
SUPINE				
RESTING HEART RATE (bpm)	82+4	76+5	80+3	0.05
RESTING SYSTOLIC BP (mmHg)	128+10	119+14	126+11	0.01
RESTING DIASTOLIC BP (mmHg)	77+8	69+9	77+7	0.01
ERECT				
RESTING HEART RATE (bpm)	84+4	81+6	83+5	ns
RESTING SYSTOLIC BP (mmHg)	127+9	105+16	125+8	0.001
RESTING DIASTOLIC BP (mmHg)	81+8	67+10	78+9	0.001
SLOW PROTOCOL				
EXERCISE HEART RATE (bpm)	120+16	121+14	122+15	ns
EXERCISE SYSTOLIC BP (mmHg)	136+23	120+21	141+20	0.002
EXERCISE DOUBLE PRODUCT	16.3+5.1	14.9+4.1	17.2+4.5	0.01
EXERCISE TIME (minutes)	8.7+3.1	9.6+2.4	10.9+3.3	ns
MAXIMUM OXYGEN CONSUMPTION (ml/kg/minute)	12.5+2.7	12.9+3.1	13.6+2.9	ns
FAST PROTOCOL				
EXERCISE HEART RATE (bpm)	130+14	133+13	132+13	ns
EXERCISE SYSTOLIC BP (mmHg)	144+18	123+16	148+19	0.001
EXERCISE DOUBLE PRODUCT	18.7+4.3	16.4+4.0	19.5+4.1	0.01
EXERCISE TIME (seconds)	234+22	213+18	255+24	0.01
MAXIMUM OXYGEN CONSUMPTION (ml/Kg/minute)	15.4+3.6	14.9+3.0	15.7+3.1	ns **

BP = blood pressure
bpm = beats per minute

** maximum oxygen consumption achieved was consistantly higher ($p<0.05$) on the fast protocol.

TABLE 19.2 SUPINE BICYCLE EXERCISE

	BASELINE	CAPTOPRIL	PLACEBO	p<
RESTING EJECTION FRACTION (%)	24+8	24+10	25+8	ns
EXERCISE HEART RATE (bpm)	118+19	122+17	124+20	ns
EXERCISE SYSTOLIC BP (mmHg)	137+19	132+16	140+13	0.05
EXERCISE DOUBLE PRODUCT	16.2+3.7	16.1+2.8	17.4+3.9	ns
EXERCISE EJECTION FRACTION (%)	19+5	17+7	17+6	ns
EXERCISE TIME (seconds)	221+36	257+28	232+24	ns

BP = blood pressure

Respiratory Gas Analysis

Maximal oxygen consumption was consistently greater with the shorter "FAST" protocol. Maximal oxygen consumption did not vary between placebo and captopril phases.

Radionuclide Ventriculography (Table 19.3)

Left ventricular ejection fraction fell during exercise, consistent with myocardial ischaemia. Resting and exercise left ventricular ejection fractions were unaltered by captopril as was the exercise-induced change. There was a statistically insignificant trend to improved exercise performance during captopril therapy. Eight patients stopped with angina, 6 of whom also complained of breathlessness and 6 with leg fatigue during placebo, and 10 with angina, 3 of whom also complained of breathlessness, and 4 with leg fatigue on captopril. Exercise heart rate was similar on captopril and placebo, but exercise systolic blood pressure was lower. Comparing exercise tests on captopril and placebo, there was a significant difference between the change in exercise performance when supine bicycle exercise (+11% in favour of captopril) and either upright treadmill protocol was used (-12% and -17%;$p<0.05$). The reduction in peak exercise systolic blood pressure on captopril was also less marked in the supine position ($p<0.05$).

TABLE 19.3 BIOCHEMISTRY

n = 16

	BASELINE	CAPTOPRIL	PLACEBO	p<
SERUM SODIUM (mmol/L)	137+5	136+3	136+3	ns
SERUM POTASSIUM (mmol/L)	3.5+0.6	4.0+0.4	3.4+0.7	0.01
SERUM UREA (mmol/L)	7.7+3.6	8.9+5.4	7.4+4.0	0.05
SERUM CREATININE (umol/L)	113+24	121+19	112+18	ns

n = 9

PLASMA ACTIVE RENIN CONCENTRATION (uU/ml)				
MEAN	298	2118	214	
MEDIAN	144	2294	112	
RANGE	5-1040	14-5234	5-720	0.001

PLASMA ANGIOTENSIN II (pmol/L)				
MEAN	118	21	89	
MEDIAN	70	17	42	
RANGE	12-308	2-29	10-288	0.001

PLASMA NORADRENALINE (nmol/L)				
MEAN	6.4	4.4	6.5	
MEDIAN	6.1	3.9	5.9	
RANGE	2.5-13.4	1.4-8.9	1.9-12.7	0.05

Ambulatory Electrocardiographic Monitoring (Table 19.4)

The frequency of isolated ventricular extrasystoles and salvoes was reduced, but the decline in ventricular function was not statistically significant.

Comparison of Patients by clinical preference

Patients receiving concomitant therapy with nifedipine (n=3) all preferred placebo and had more severe angina on captopril. The combination of nitrates and captopril (5 patients) did not exhibit the same deleterious effects. Those patients who had a large fall in systolic blood pressure on captopril also did worse. Of the 9 patients who had a stated preference for placebo, the resting diastolic arterial pressure fell by a mean of 23%, while of 3 who preferred captopril it fell by only 4%. Baseline plasma active renin concentrations tended to be higher in the former group (median value 162 uU/l v 10 uU/l). Among the 14 patients who had angiography, 8 had coronary stenoses in vessels supplying actively contracting regions at rest (group A). Six had stenoses only in vessels supplying regions with severe wall motion abnormalities (group B). Six of eight patients in group A preferred placebo and two had no preference, while only two of six patients in group B preferred placebo, and one had no preference.

TABLE 19.4 AMBULATORY MONITORING
(EVENTS OVER 48 HOURS)

	BASELINE	CAPTOPRIL	PLACEBO	p<
VENTRICULAR EXTRASYSTOLES				
MEAN	4628	3478	5088	
MEDIAN	1144	686	1424	
RANGE	126-19,728	0-13,084	342-16,024	0.05
VENTRICULAR SALVOES				
MEAN	24	14	28	
MEDIAN	6	2	6	
RANGE	0-128	0-102	0-164	0.05
VENTRICULAR TACHYCARDIA				
MEAN	6	3	4	
MEDIAN	1	0	0	
RANGE	0-42	0-24	0-32	ns

CHAPTER 20: MORTALITY IN HEART FAILURE: CLINICAL VARIABLES OF PROGNOSTIC VALUE AND THE IMPACT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Chronic heart failure is a condition of varied aetiology that imposes a heavy burden of symptoms, confers a very poor prognosis,[738-740] and affects 4% of the population under the age of 75 years.[741] Once an in-hospital diagnosis of heart failure has been made, the annual mortality is likely to be 40% or more,[738-740] though the prognosis seems to be slightly better in those patients not referred to hospital and who, presumably, have milder disease.

The most frequently reported mode of death in patients with heart failure seems to be sudden,[739,740,742] presumably caused by ventricular arrhythmias[743] which are common.[738,744,745] Many[738,746,747] but not all[748-750] workers suggest that these arrhythmias are powerful independent prognostic indicators for mortality. Whether they are of primary importance or merely reflect the extent of left ventricular dysfunction is unclear at present.[738,747,750] One retrospective case-control study suggested no reduction in mortality with procainamide,[751] though anecdotal comment has suggested a possible benefit with amiodarone.[752] Another prospective study suggested that arrhythmias in patients with heart failure are resistant to treatment.[753] "Vasodilator" treatment on the other hand has been shown to improve outcome.[754,755]

We investigated the importance of arrhythmias, ventricular function, treatment, functional capacity, and biochemical indices in predicting outcome in a large series of patients with heart failure followed prospectively in an open study.

PATIENTS

The patients presented in Chapter 10 are a sub-set from this larger population who had more detailed studies on their metabolic and neuroendocrine profile carried out. One hundred and fifty two patients in whom a diagnosis of heart failure was established on clinical, radiological, and echocardiographic grounds were recruited. All were symptomatically stable but in New York Heart Association Classes II-IV (mean$\pm$SD) 2.8(0.8). The mean ($\pm$SD) age was 59 (9) years, 84% were male, and the mean ($\pm$SD) duration of heart failure was 18 (19) months (all >3 months).

One hundred and four had received digoxin for more than one month before entry to the study and all were receiving frusemide in a mean (SD) daily dose of 127 (85) mg/day. No patients were on potassium-sparing diuretics but 47 were on potassium chloride supplements (median dose 1800 mg/day).

The diagnosis was ischaemic heart disease in 93, idiopathic congestive (dilated) cardiomyopathy in 28, residual left ventricular dysfunction after successful valve replacement in 16, secondary to hypertension in 9, and alcohol-related cardiomyopathy in 6. Patients in whom angina was an

appreciable complaint at rest or during exercise were excluded. The absence of coronary artery disease was always confirmed by coronary angiography; coronary artery disease was diagnosed either at coronary angiography or after myocardial infarction with typical history and electrocardiographic and enzyme changes.

Patients were allocated to angiotensin-converting enzyme inhibitors or amiodarone on an open basis for clinical reasons on the order of the attending physician or in the context of a clinical trial. Selection of patients was not systematic and criteria varied over the period of observation. Patients were therefore not necessarily selected for angiotensin-converting enzyme inhibitors or treatment with amiodarone on the basis of severity of heart failure or the presence of arrhythmias. This reflects the uncertainty of the clinical value of these drugs during much of the observation period. Amiodarone was started at 600 mg a day in most cases, with a mean (±SD) daily maintenance dose of 183(54) mg/day (range 100-400 mg/day).

METHODS

New York Heart Association scores were determined in the light of exercise performance. Heart rate was measured from the apex beat and blood pressure was recorded with a Hawksley random zero sphygmomanometer.

A 12-lead electrocardiogram was recorded before a graded

treadmill test using a modified Bruce protocol. Forty-eight hour ambulatory monitoring was also performed with a Medilog I system, and the results were analysed with a Pathfinder Analyser under constant visual monitoring. Ventricular tachycardia was defined as >3 consecutive ventricular extrasystoles at >120 beats/minute.

M-mode echocardiography was performed with the patients in the left lateral position.

Blood was taken for measurement of serum sodium, potassium, and creatinine concentrations on at least 2 and up to 5 occasions at different times of day and an average value was taken. The median number of samples taken was 3. Blood was taken for measurement of serum digoxin concentration at least 6 hours after the last dose.

DEFINITIONS OF MODES OF DEATH

The mode of death was ascertained either from the deceased's relatives, from the family practitioner, or from the observations of the hospital staff. Where death was believed to be from cardiac causes, it was classified as death from pulmonary oedema, cardiogenic shock, or sudden (defined as death without reporting a change in symptoms to lay or medical persons in the 24 hours before death). Sudden death was also divided into cases that had or had not indicated some gradual chronic deterioration of symptoms of heart failure in the months before death.

STATISTICAL ANALYSIS

Means (±SD) are given for the study group and treatment subgroups. Means of subgroups were compared by two- sample t-tests. The log-rank test was used to compare survival rates in the treatment subgroups. Cox's proportional hazards model was used to correct for and identify important co-variates. A stepwise routine was used to identify the best subset of predictors. Both forward and backward stepping was used to protect against the omission of important predictors. Pearsons' product moment correlation coefficients were calculated to investigate inter-relations between the prognostic indicators and the other variables. Estimated survival curves were subsequently constructed for each treatment and for each of the variables independently related to outcome. This was done by fixing at median values all variables that carried independent predictive information other than the one tested.

RESULTS

Clinical Outcome

The mean follow up time was 21 (12) months, during which 63 patients (41%) died. Forty-seven (75%) of the deaths were sudden, though in 12 (26%) patient's clinical deterioration was noted at the follow-up clinic in the months before death. Five patients died in cardiogenic shock after recurrent myocardial infarction, and 2 died after cerebrovascular accidents. One patient died after

mesenteric artery occlusion, one soon after peripheral vascular surgery, one from chronic lymphatic leukaemia and associated respiratory infection, and one from rectal carcinoma. Only 5 (8%) deaths were considered to be caused by intractable left ventricular failure. Four patients presented with sustained ventricular tachycardia during follow up. None was on anti- arrhythmic treatment at the time. Although treatment with procainamide in 2 cases, tocainide in one case, and amiodarone in one case, was started, all four subsequently died.

Prevalence of Arrhythmias

The mean frequency of ventricular extrasystoles over 24 hours was 4321 (median value 1375, range 0-24,299). Seventy-nine per cent of patients had couplets or salvoes of ventricular extrasystoles on ambulatory monitoring (mean 15, median 5, range 0-768 per 24 hours). Sixty one per cent of patients had one or more episode of ventricular tachycardia with a mean overall frequency of 7 (median value 2, range 0-201) in 24 hours.

Baseline Characteristics

The mean initial heart rate was 88 (14) beats/minute and mean arterial pressure was 91 (14) mm Hg. Forty-five patients (30%) had left bundle branch block. The mean concentration of serum sodium was 136 + 10 mmol/l, of serum potassium 3.8 (0.4) mmol/l, and of serum creatinine 117 (27) umol/l. The mean end-diastolic left ventricular

dimension was 6.7 (0.8) cm and end-systolic dimension was 5.7 (0.9) cm. The resulting fractional shortening was 15.3 (6.5).

Changes in Treatment

During follow up, 11 patients were started on nitrate treatment, one on prazosin, and 3 on hydralazine. In 18 patients an increase in diuretic treatment was required, and in 6 patients who were taking angiotensin-converting enzyme inhibitors the dose of diuretic was reduced because of postural hypotension. As mentioned above, 4 patients were treated with anti-arrhythmic agents for sustained ventricular tachycardia at a time other than entry to the study. Nineteen patients were taking potassium-sparing diuretics: amiloride in 14 (10-20 mg/day) and spironolactone in 5 (25-50 mg/day). Only 3 of these were in the group treated with angiotensin- converting enzyme inhibitors.

Comparison of Treatment Subgroups

Those treated with amiodarone were well matched in all respects with those who did not receive this treatment. **(Table 20.1)** Those subjects treated with angiotensin-converting enzyme inhibitors **(Table 20.2)** had significantly worse New York Heart Association scores, tended to have shorter exercise times, more episodes of ventricular tachycardia, and required significantly more frusemide and digoxin. Patients taking digoxin **(Table 20.3)** had worse New

Table 20.1

	NO AMIODARONE	AMIODARONE
n=	111	41
AGE(years)	60+10	58+8
SEX(%males)	82%	88%
NYHA	2.8+0.8	2.9+0.9
C.A.D.(%)	60%	66%
EXERCISE TIME (mins)	7.5+4.8	7.4+4.6
M.A.P.(mmHg)	91+14	92+14
F.S.(%)	15.6+6.8	14.6+5.7
LEFT BBB(%)	32%	24%
SERUM SODIUM (mmol/L)	137+5	137+4
SERUM POTASSIUM (mmol/L)	3.8+0.4	3.9+0.4
VENTRICULAR EXTRASYSTOLES (/24hrs) range	4261 6-24299	4462 7-17345
VENTRICULAR TACHYCARDIA (24hrs) range	4.8 0-67	11.4 0-201
ACE INHIBITOR(n)	43	18
DIGOXIN(n)	74	30
FRUSEMIDE(mg/day)	128+93	122+61

VALUES ARE MEAN + STANDARD DEVIATION OR RANGE GIVEN IN BRACKETS ( ).
ACE = ANGIOTENSIN CONVERTING ENZYME
NYHA = NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS
C.A.D. = CORONARY ARTERY DISEASE
M.A.P. = MEAN ARTERIAL PRESSURE
F.S. = ECHOCARDIOGRAPHIC LEFT VENTRICULAR FRACTIONAL SHORTENING
BBB = BUNDLE BRANCH BLOCK

Table 20.2

	NO ACE INHIBITOR		ACE INHIBITOR
n=	91		61
AGE(years)	59+10		59+8
SEX(%males)	89%		75%
NYHA	2.6+0.7	p<0.01	3.1+0.8
C.A.D.(%)	65%		56%
EXERCISE TIME (mins)	8.0+4.5		6.6+5.0
M.A.P.(mmHg)	93+15		88+13
F.S.(%)	16.1+6.3		14.3+6.7
LEFT BBB(%)	32%		27%
SERUM SODIUM (mmol/L)	137+8		136+6
SERUM POTASSIUM (mmol/L)	3.9+0.4		3.7+0.4
VENTRICULAR EXTRASYSTOLES (/24hrs) range	4121 0-21804		4592 0-24299
VENTRICULAR TACHYCARDIA (24hrs) range	4.4 0-38		10 0-201
AMIODARONE(n)	23		18
DIGOXIN(n)	49	p<0.05	55
FRUSEMIDE(mg/day)	101+54	p<0.001	163+106

VALUES ARE MEAN + STANDARD DEVIATION OR RANGE GIVEN IN BRACKETS ( ).
ACE = ANGIOTENSIN CONVERTING ENZYME
NYHA = NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS
C.A.D. = CORONARY ARTERY DISEASE
M.A.P. = MEAN ARTERIAL PRESSURE
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BBB = BUNDLE BRANCH BLOCK

Table 20.3

	NO DIGOXIN		DIGOXIN
n=	48		104
AGE(years)	59+11		60+9
SEX(%males)	89%		80%
NYHA	2.5+0.7	p<0.03	3.0+0.8
C.A.D.(%)	50%		67%
EXERCISE TIME (mins)	8.0+4.5		7.0+4.7
M.A.P.(mmHg)	93+13		90+15
F.S.(%)	16.6+6.3		14.8+6.5
LEFT BBB(%)	37%		29%
SERUM SODIUM (mmol/L)	138+5		136+5
SERUM POTASSIUM (mmol/L)	4.0+0.4		3.8+0.4
VENTRICULAR EXTRASYSTOLES (/24hrs) range	3452 6-21804		4692 7-24299
VENTRICULAR TACHYCARDIA (24hrs) range	4.7 0-38		7.6 0-201
AMIODARONE(n)	11		30
ACE INHIBITOR(n)	6	p<0.01	55
FRUSEMIDE(mg/day)	93+58		143+92

VALUES ARE MEAN + STANDARD DEVIATION OR RANGE GIVEN IN BRACKETS ( ).
ACE = ANGIOTENSIN CONVERTING ENZYME
NYHA = NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS
C.A.D. = CORONARY ARTERY DISEASE
M.A.P. = MEAN ARTERIAL PRESSURE
F.S. = ECHOCARDIOGRAPHIC LEFT VENTRICULAR FRACTIONAL SHORTENING
BBB = BUNDLE BRANCH BLOCK

York Heart Association scores than those not on digoxin.

Predictors of Prognosis

Several variables were found to be of prognostic value by Cox's proportional hazards model. **(Table 20.4)** Stepwise regression with Cox's proportional hazards model showed that, in order of importance, ventricular extrasystoles ($p<0.0001$), amiodarone treatment ($p<0.001$), mean blood pressure ($p<0.001$), and a diagnosis of coronary artery disease ($p<0.001$) were of important independent prognostic value. Initial serum potassium concentration ($p<0.02$) and exercise time ($p<0.03$) were found to be of some additional independent predictive value.

Predictive Value

Amiodarone treatment seemed to improve the prognosis ($p<0.01$) **(Figure 20.1)**; this reduction in mortality was largely caused by a decline in the occurrence of sudden death, as 45% of those not treated with amiodarone died suddenly compared with 15% of those treated with amiodarone during the follow up period. While angiotensin-converting enzyme inhibitors had no overall beneficial effect on mortality **(Figure 20.2)**, the frequency of sudden death was less (21% v 37%);$p<0.05$). There were 6 (10%) deaths (see above) caused by vascular events in the group on angiotensin-converting enzyme inhibitors but only 3 (3%) in the group not treated with angiotensin-converting enzyme inhibitors (NS). Treatment with digoxin **(Figure 20.3)** and

Table 20.4

PREDICTORS OF PROGNOSIS ON UNIVARIATE ANALYSIS	
VENTRICULAR EXTRASYSTOLES (24HRS)	$p<0.0001$
MEAN ARTERIAL PRESSURE (mmHg)	$p<0.0001$
SERUM POTASSIUM (mmol/L)	$p<0.0001$
SERUM SODIUM (mmol/L)	$p<0.0001$
EXERCISE TIME (minutes)	$p<0.0001$
NYHA SCORE	$p<0.0001$
AMIODARONE THERAPY	$p<0.01$
ECHO END-SYSTOLIC DIMENSION (cm)	$p<0.01$
ECHO FRACTIONAL SHORTENING (%)	$p<0.01$
LEFT BUNDLE BRANCH BLOCK	$p<0.01$
ECHO END-DIASTOLIC DIMENSION (cm)	$p<0.02$
DIAGNOSIS OF CORONARY ARTERY DISEASE	$p<0.06$
VENTRICULAR TACHYCARDIA (/24hours)	$p<0.06$
AGE(years)	$p<0.07$
FRUSEMIDE DOSE (mg/day)	$p<0.1$
DURATION OF SYMPTOMS	$p<0.7$
HEART RATE (bpm)	$p<0.8$
CAPTOPRIL THERAPY	$p=0.93$
DIGOXIN THERAPY	$p=0.99$

Figure 20.1 Cumulative proportion surviving

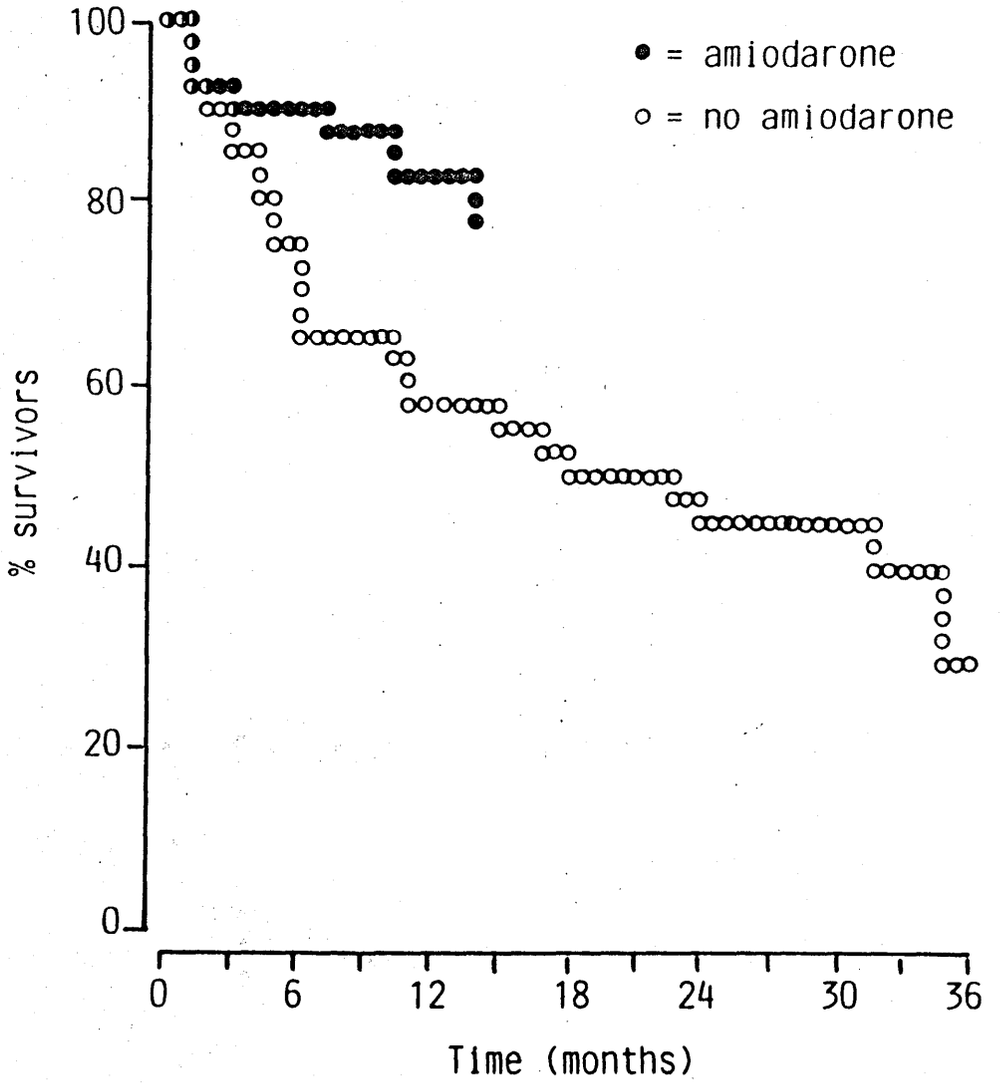


Figure 20.2 Cumulative proportion surviving

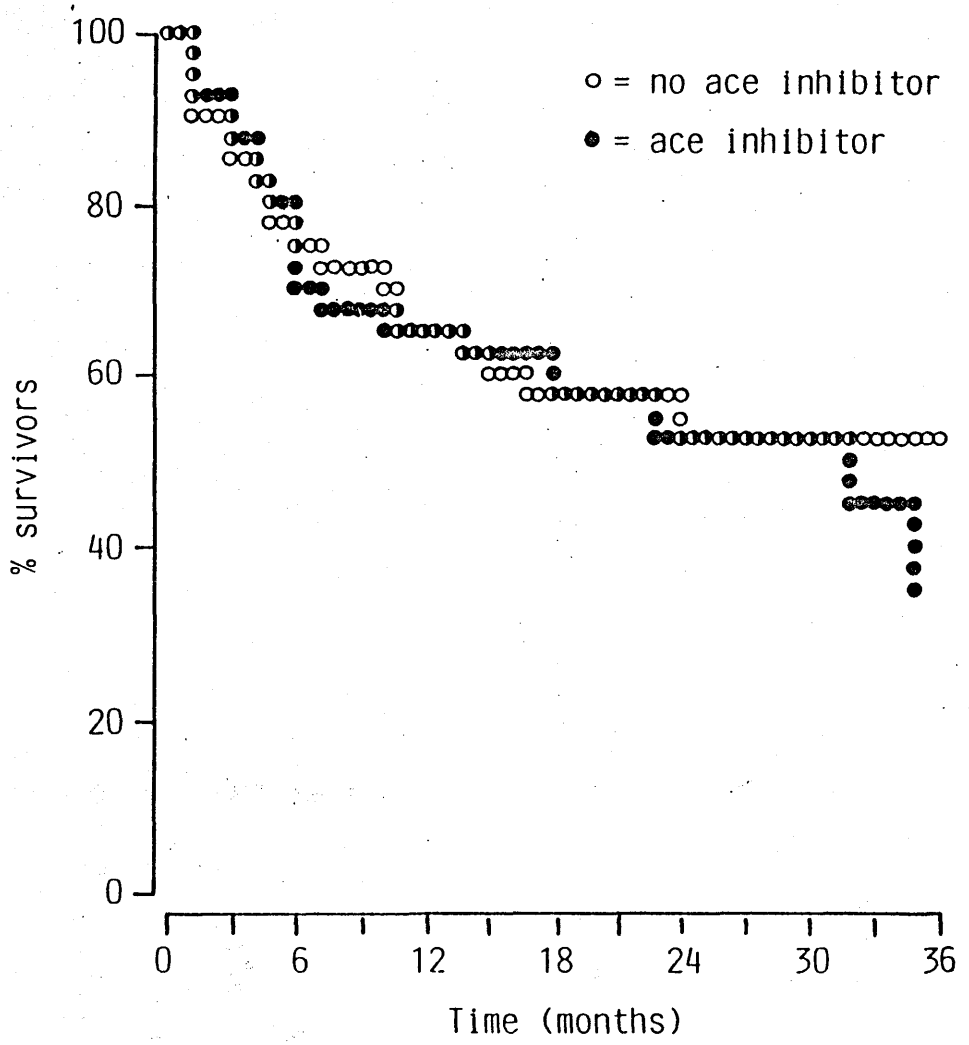
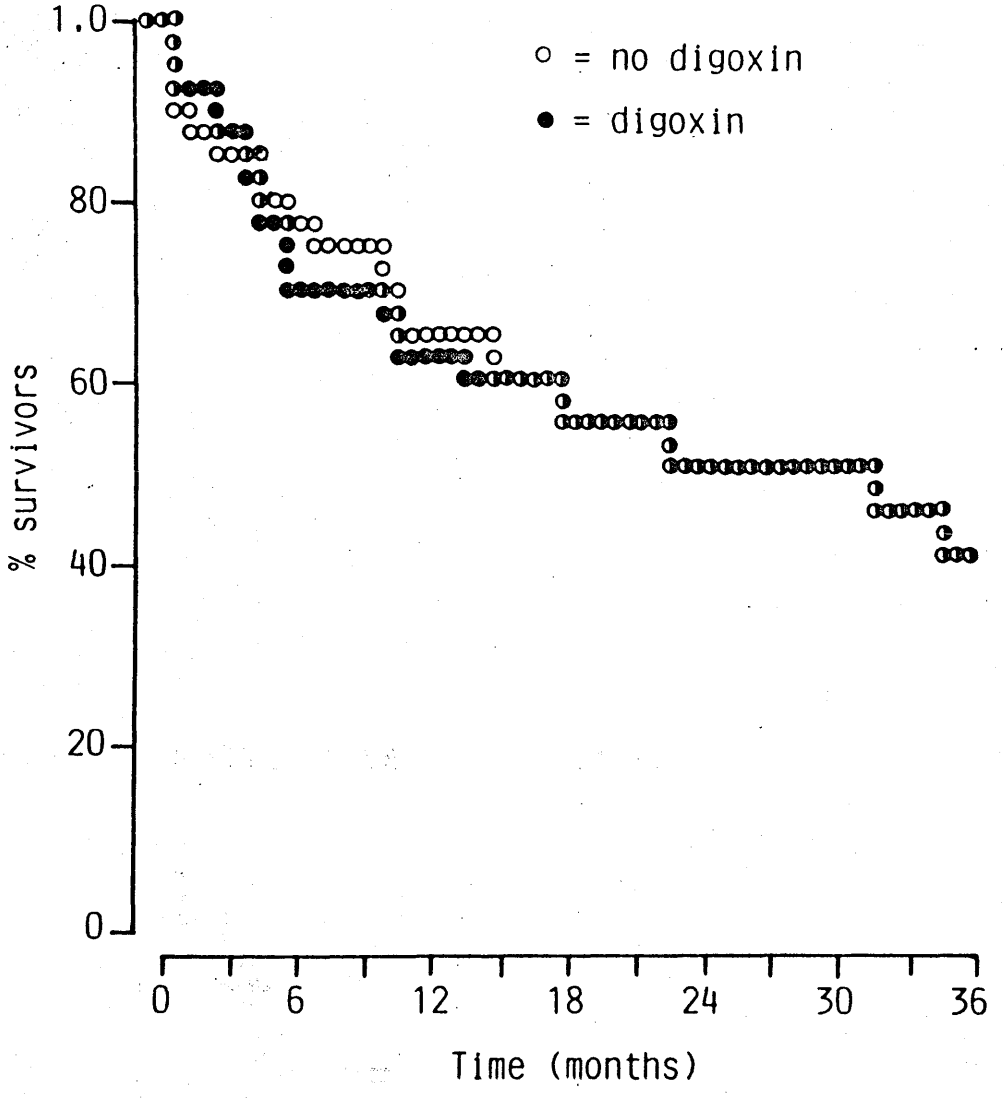


Figure 20.3 Cumulative proportion surviving



diuretic dose did not alter the overall prognosis or the frequency of sudden death before or after adjustment for the co-variates. Separate analysis of those patients undergoing a change in treatment showed no alteration in prognosis. Potassium supplements did not affect prognosis.

Relation of Ventricular Extrasystoles to other measured variables

Ventricular extrasystoles were correlated with the frequency of more complex ventricular extrasystoles ($r=0.66;p<0.0001$) and were also associated with a worse New York Heart Association score ($p<0.001$). However, no association was noted with the use of digoxin or with the concentrations of serum digoxin (0.8-23 nmol/l) (all of which were in the therapeutic range <2.6 nmol/l). Exercise time ($r=-0.45;p<0.001$), serum potassium ($r=-0.38;p<0.001$), and left bundle branch block ($r=0.35;p<0.001$) were the best predictors of the frequency of ventricular arrhythmias.

Comparison of Risk Factors in Diagnosis Subgroups

Those subjects with heart failure caused by coronary artery disease had a significantly lower blood pressure than those without coronary artery disease (89 (12) v 94 (16) mm Hg;$p<0.01$) and a lower frequency of ventricular arrhythmias (3950 v 4875/24 hours;$p<0.02$). The duration of symptoms before entry was also shorter (12.9 (14.7) v 25.7 (21.1) months;$p<0.01$). In other respects, including ventricular function (fractional shortening 15.5 (6.3)% v 15.0 (6.8)%,

exercise time (7.5(4.6) v 7.4(4.9) minutes), and serum potassium (3.9 (0.4) v 3.8 (0.4) mmol/l) they were similar to patients in other diagnostic groups.

Relation of Mean Arterial Pressure to other measured Variables

The set of variables with the best independent relation to mean arterial pressure was serum sodium ($r=0.54;p<0.001$), New York Heart Association score ($r=-0.41;p<0.001$), and end-diastolic left ventricular dimension ($r=-0.29;p<0.01$)

Relation of Serum Potassium and Exercise Time to other measured Variables

Only serum sodium ($r=0.40;p<0.001$) was found to have a significant and independent relation to serum potassium. Exercise time was best related on stepwise regression to New York Heart Association score ($r=-0.79;p<0.0001$) and fractional shortening ($r=0.31;p<0.001$).

Estimated Survival Curves

The estimated survival curves for amiodarone versus no amiodarone treatment again suggested significant improvement in survival with amiodarone **(Figure 20.4)**. The estimated survival curves still suggested no pronounced beneficial effect with angiotensin-converting enzyme inhibitors **(Figure 20.5)**, but also suggested no deleterious effect with digoxin use. The estimated survival curves for prognostic indicators suggested that clinically meaningful

Figure 20.4 Estimated survival function

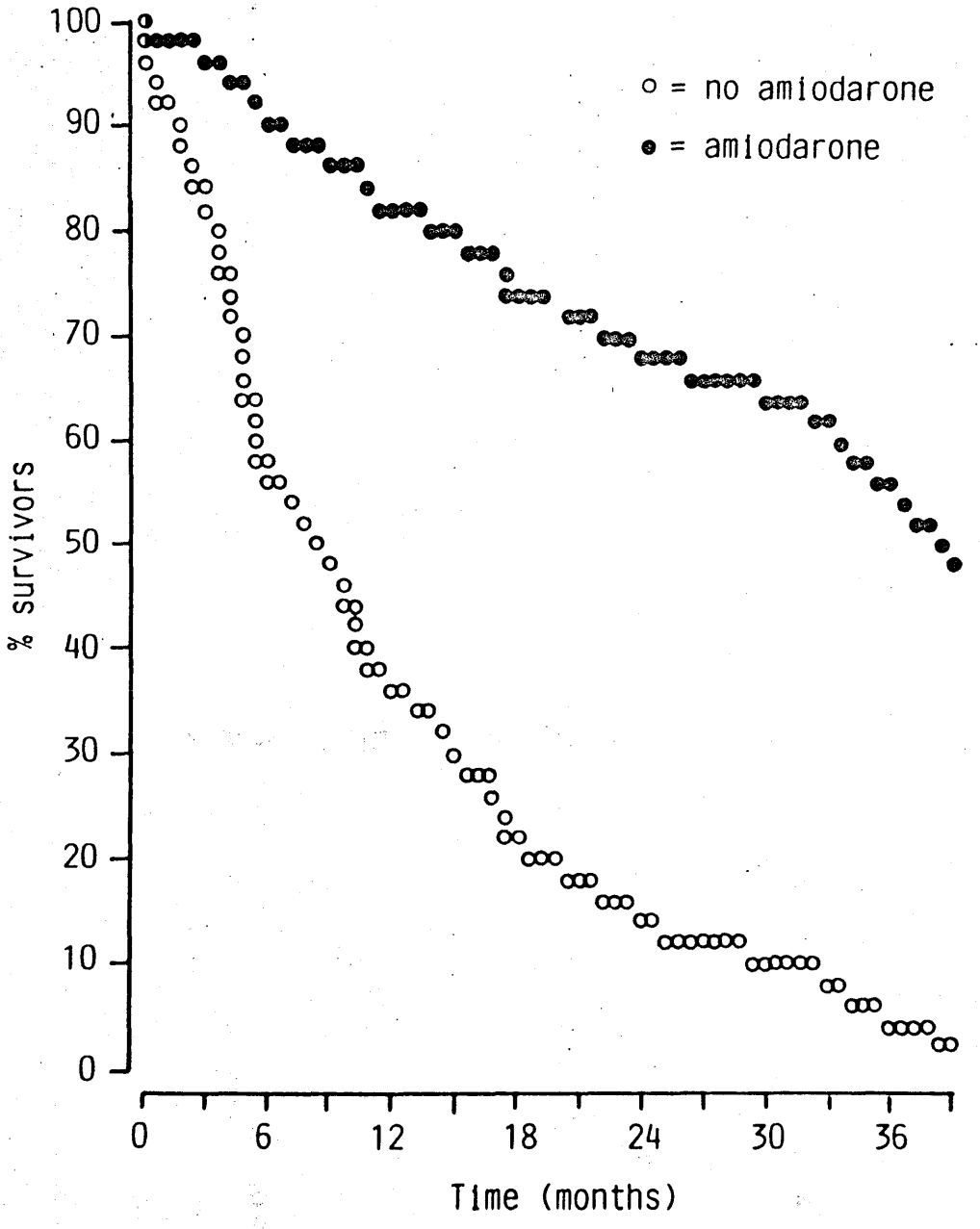
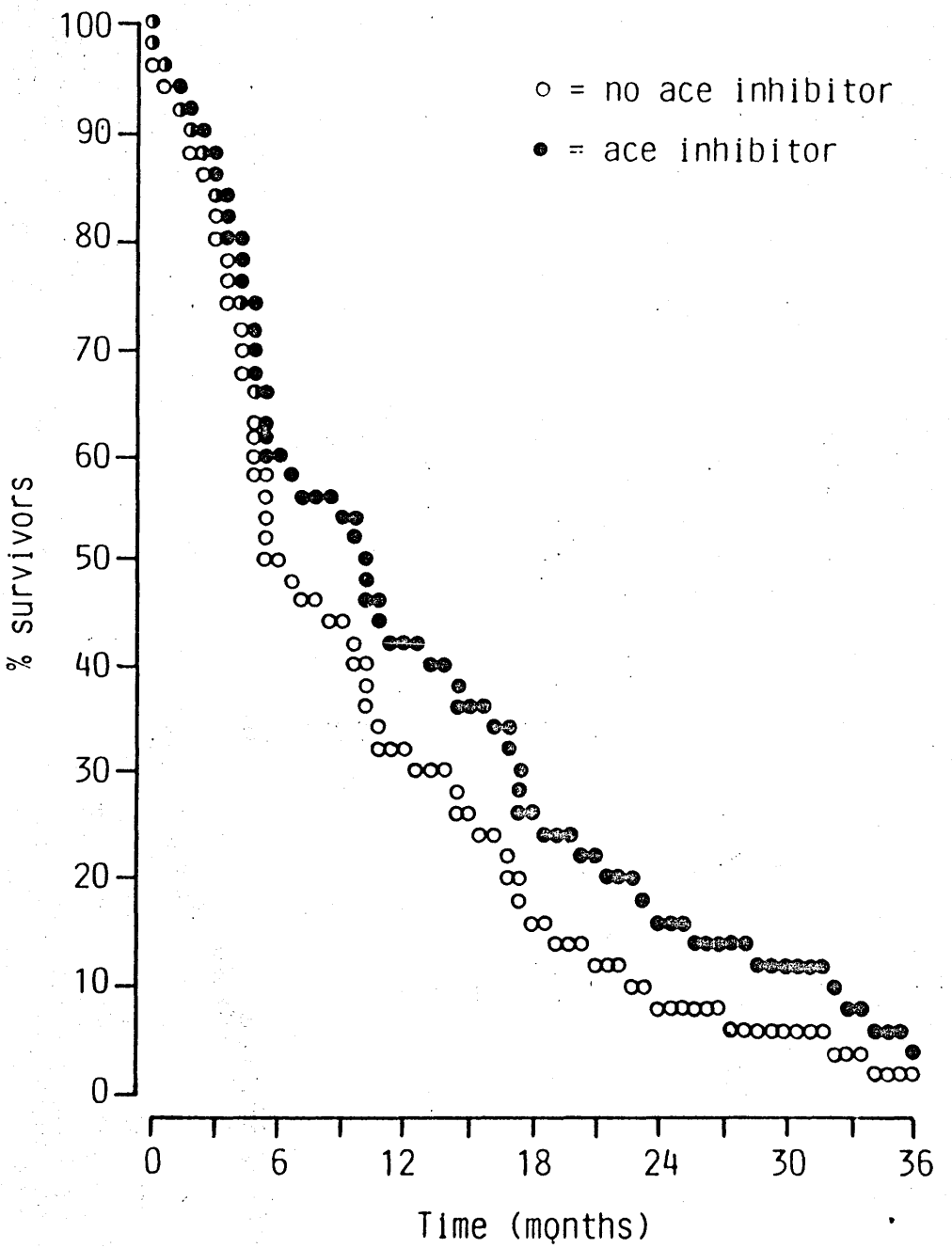


Figure 20.5 Estimated survival function



separation could be made on the basis of the frequency of ventricular extrasystoles **(Figure 20.6)**, a diagnosis of coronary artery disease **(Figure 20.7)**, mean arterial pressure **(Figure 20. 8)**, exercise time **(Figure 20.9)**, and serum potassium **(Figure 20.10)**.

Figure 20.6 Estimated survival function

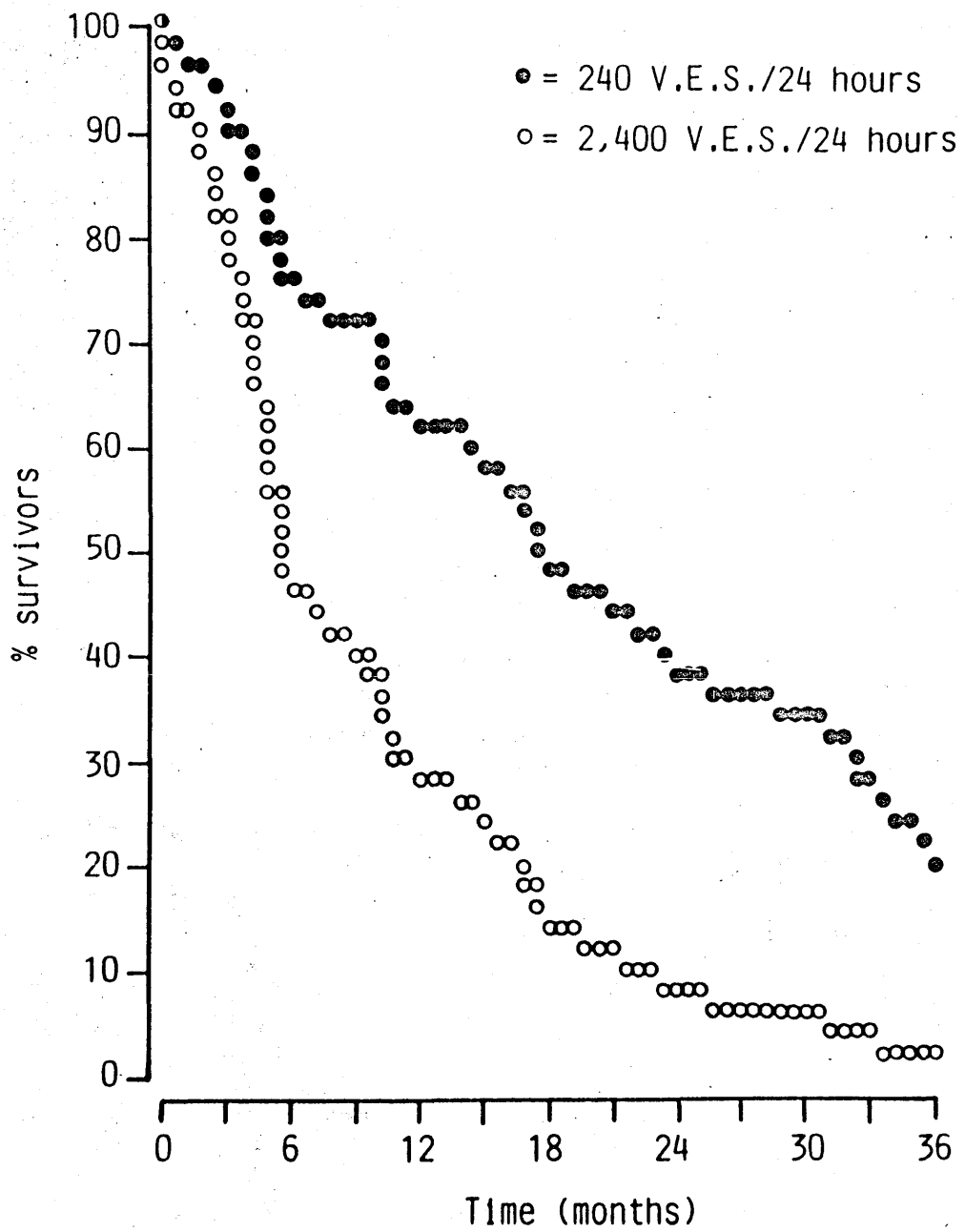


Figure 20.7

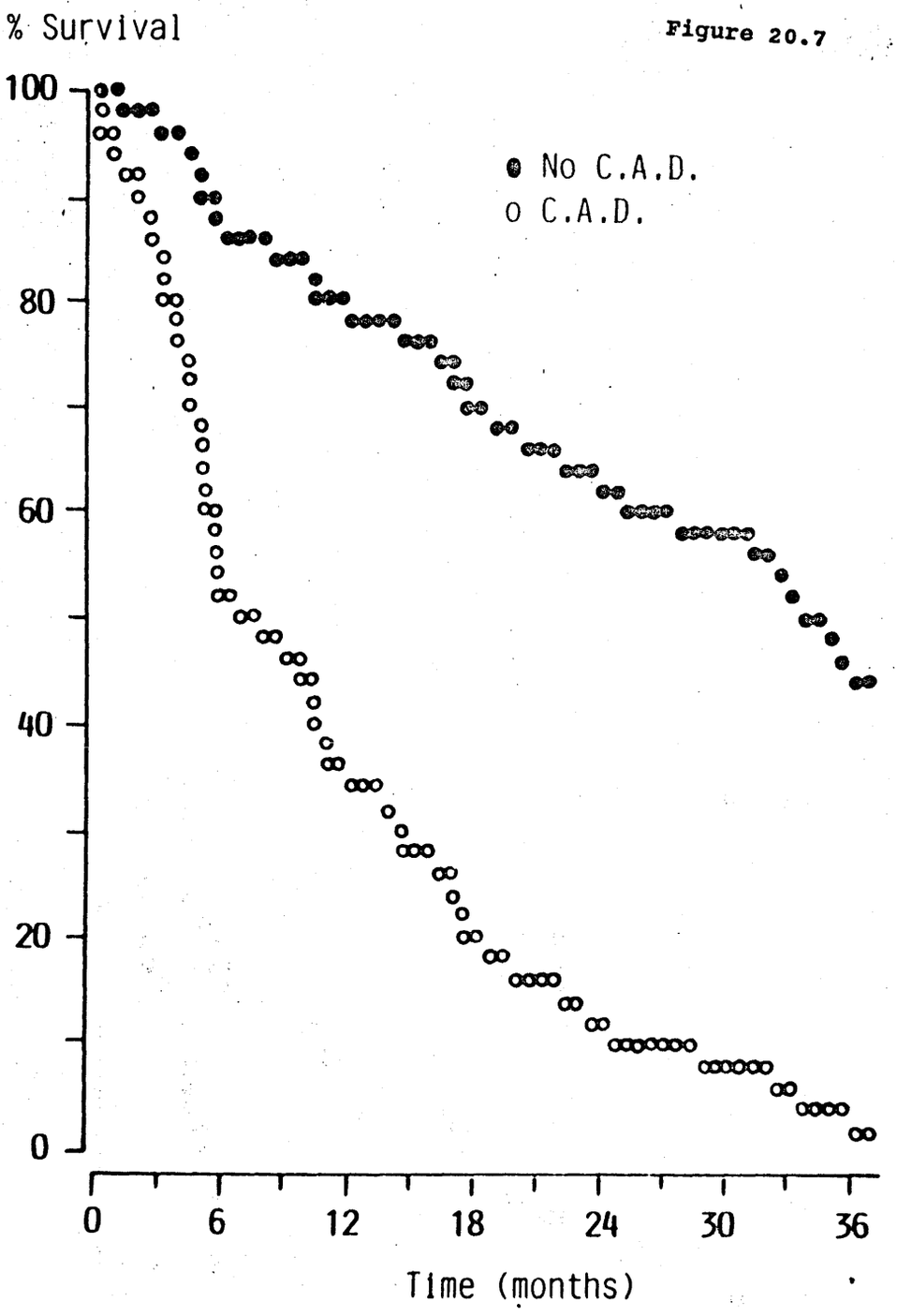

% Survival
100
80
60
40
20
0
● No C.A.D.
o C.A.D.
0
6
12
18
24
30
36
Time (months)

Figure 20.8 Estimated survival function

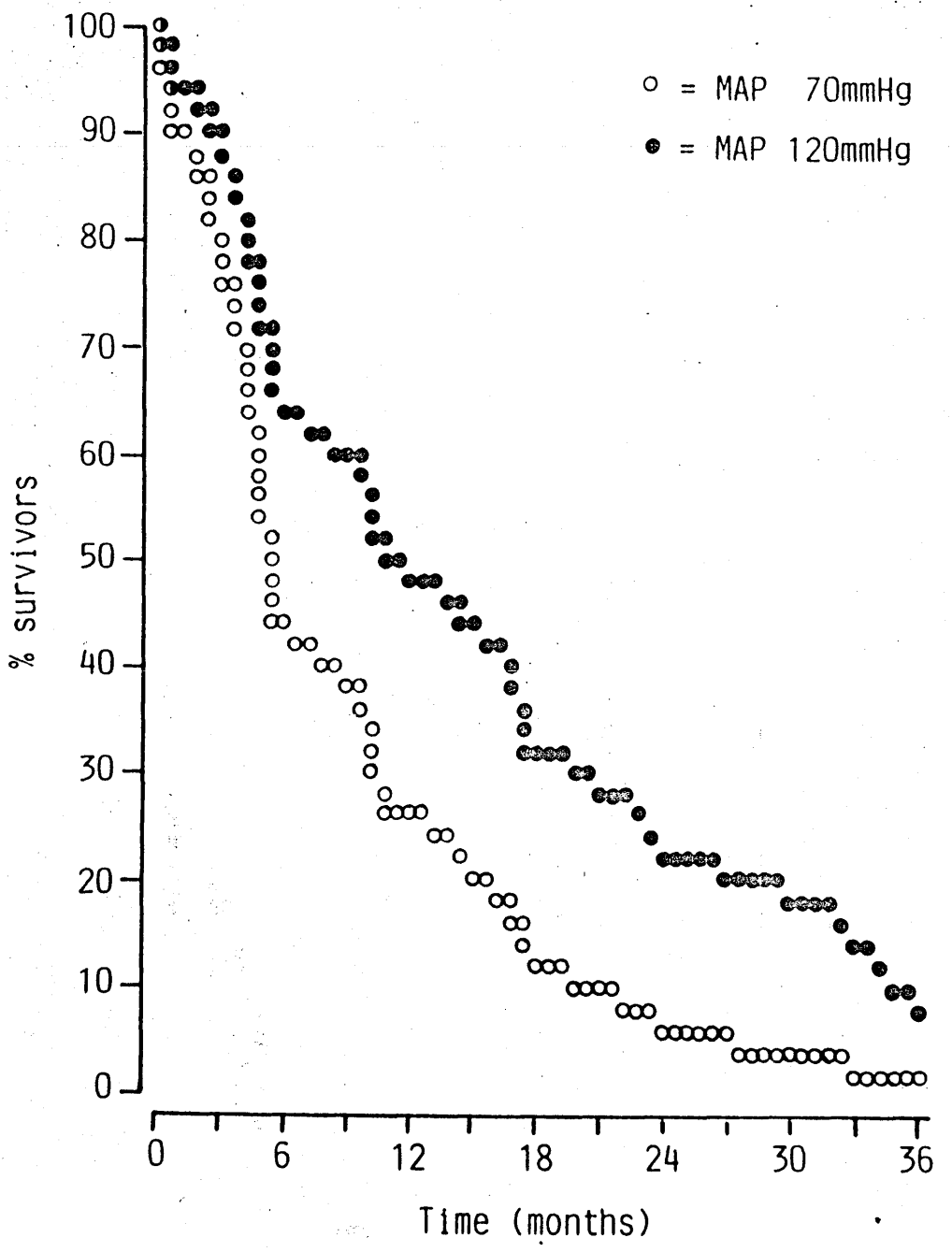


Figure 20.9 Estimated survival function

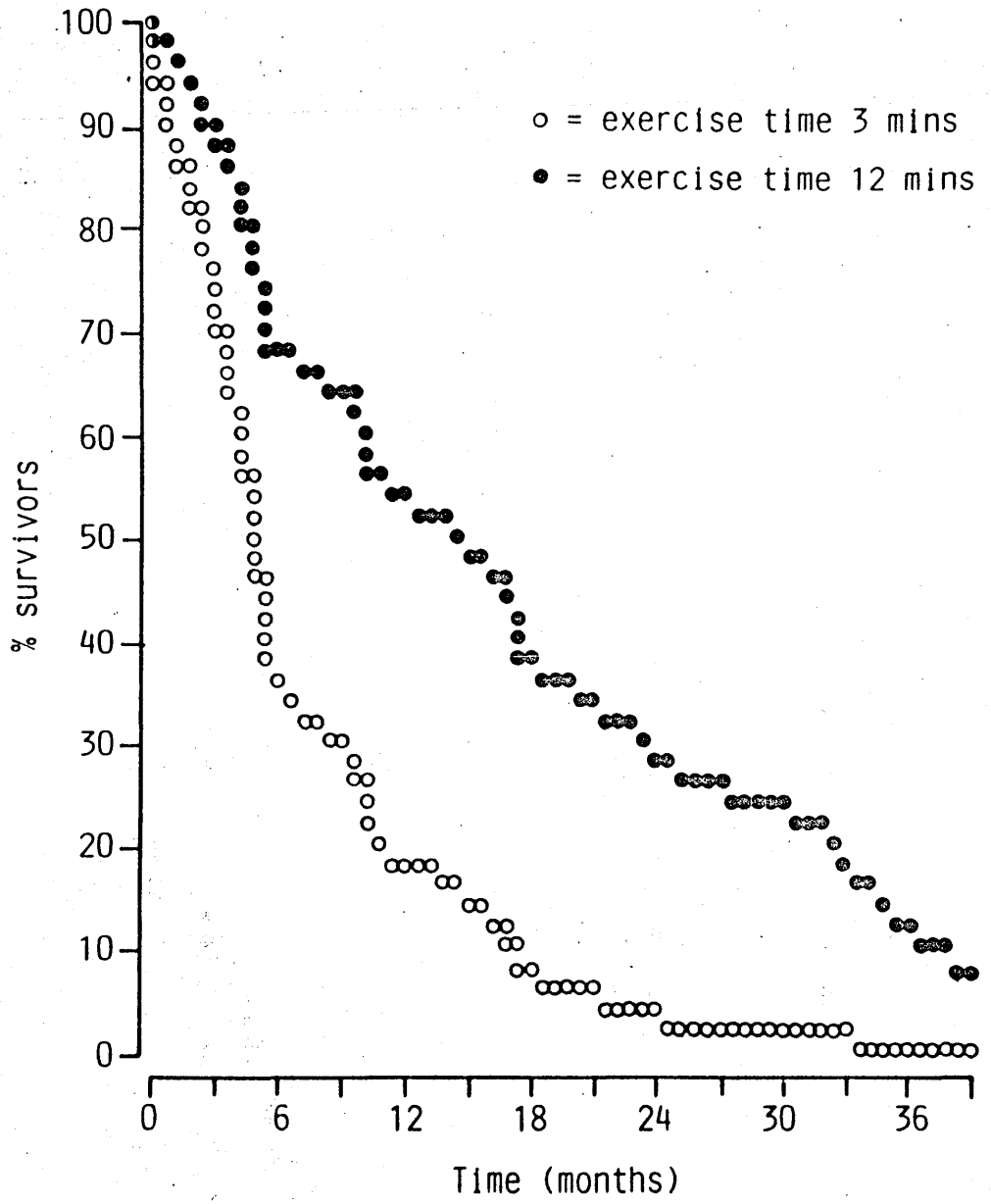
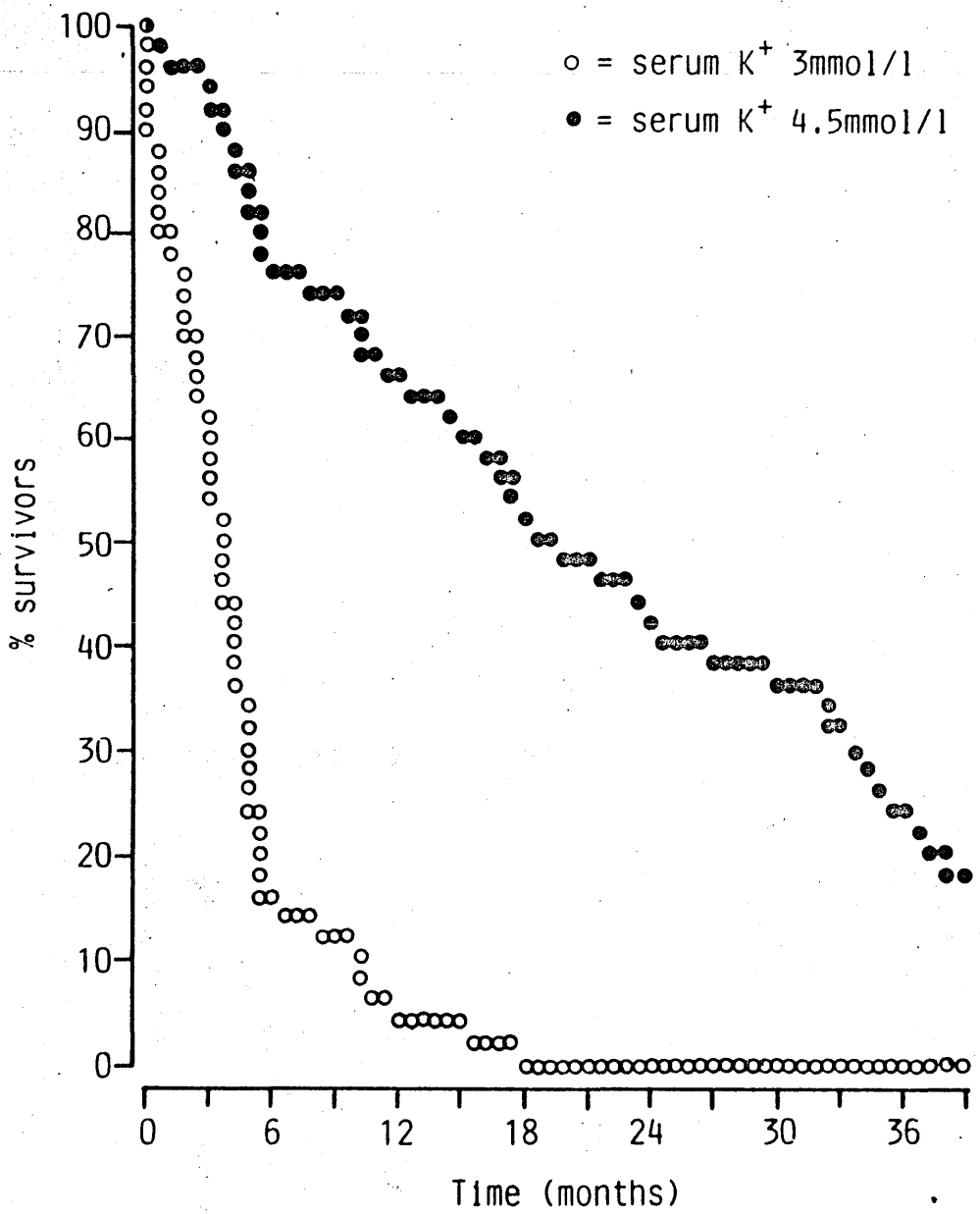


Figure 20.10 Estimated survival function



NEURO-ENDOCRINE ACTIVATION AND INHIBITION IN HEART FAILURE

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DEDICATION

To My Mother and My Wife without who waited patiently for the completion of this work.

SUMMARY

The idea of vasodilator therapy for heart failure has been toyed with for almost one hundred years, possibly more. In the mid-twentieth century nitrates attained a definite role in the management of acute pulmonary oedema. There is little doubt that vasodilators can improve central haemodynamics acutely. However, during the 1970's investigators started to apply physiological principles of preload and afterload reduction to the management of chronic heart failure. The results were largely disappointing, either because tolerance occurred to the vasodilator actions of the drugs, or because vasodilatation is an ineffective mode of treatment for chronic heart failure. When work on this thesis started disillusionment was setting in regarding the efficacy of chronic vasodilator therapy for patients with heart failure.

Although increases in plasma renin were first demonstrated in heart failure almost 50 years ago, there are few studies which have investigated the haemodynamic and metabolic correlates of renin-angiotensin-aldosterone system activation in detail. The present work indicates that patients with heart failure have a depletion of total body potassium and an excess of total body sodium when compared to normal subjects or patients with mild untreated hypertension. This depletion in potassium is not related to a reduction in lean body mass. Within the group of patients with heart failure elevated plasma concentrations of active renin were associated with a lower arterial pressure, lower serum concentrations of sodium and potassium and more

marked depletion of total body potassium. Arterial pressure appears to be an important determinant of renin secretion in heart failure. Although the electrolyte disturbances are probably largely a consequence of increased plasma concentrations of renin and angiotensin II, mediated through aldosterone and antidiuretic hormone, depletion of serum sodium and potassium may further stimulate renin secretion.

The renin-angiotensin, sympathetic and parasympathetic nervous systems are closely integrated. Angiotensin II can stimulate sympathetic activity in several ways, but can also reduce parasympathetic activity. The present work confirms that patients with heart failure have elevated sympathetic activity at rest, but reduced parasympathetic and sympathetic reflex activity as has been previously shown. This thesis also shows that at maximal exertion patients with heart failure have evidence of reduced sympathetic activity compared to normal subjects, and that this is related to the intensity rather than duration of exercise.

In view of the disturbances in haemodynamic function, autonomic activity and cellular metabolism in heart failure it is not surprising to find a high frequency of arrhythmias. These arrhythmias are directly related to plasma concentrations of renin and noradrenaline, though whether this is a causal relationship or by association with the severity of ventricular dysfunction is controversial. The present study found a poor relationship

between the severity of ventricular dysfunction and the frequency of arrhythmias in a group of patients with generally poor ventricular function.

Using two double-blind cross-over studies the angiotensin-converting enzyme inhibitors captopril and enalapril were shown to improve symptoms and exercise performance over a 6-8 week period. The study on captopril constituted one of the first placebo-controlled investigations in the literature to establish the efficacy of angiotensin-converting enzyme inhibitors in chronic heart failure. The paper on enalapril established that this was a class effect. These studies demonstrated that angiotensin-converting enzyme inhibitors could correct hypokalaemia and total body potassium depletion, but did not have a major impact on serum or total body sodium. Angiotensin-converting enzyme inhibitors also reduced plasma levels of noradrenaline, suggesting reduced sympathetic activity, and improved parasympathetic reflex responsiveness. Not surprisingly angiotensin-converting enzyme inhibitors also reduced the frequency of ventricular arrhythmias.

Studies were performed to investigate the effects of angiotensin-converting enzyme inhibitors on renal function in greater detail, and their interaction with frusemide. These indicated that introduction of angiotensin-converting enzyme inhibitor led to a reduced diuresis, plasma volume expansion and a fall in serum sodium. Urinary potassium losses were reduced and serum potassium unaltered in the short term. Renal blood flow tended to increase and

glomerular filtration rate to fall; these effects were enhanced by concomitant administration of frusemide. Studies on renal tubular function indicated increased proximal tubular water and sodium reabsorption as the likely cause for the reduced diuresis in response to frusemide. Longer term studies indicate that angiotensin-converting enzyme inhibitors cause a consistent fall in glomerular filtration rate and increase in renal blood flow while the filtration fraction is reduced towards normal. Withdrawal of the angiotensin-converting enzyme inhibitor leads to a rapid return of glomerular filtration to baseline levels, but renal blood flow appears elevated for some time after withdrawal, suggesting structural change in the vasculature or prolonged tissue enzyme inhibition.

Heart failure and angina pectoris commonly co-exist but the effects of angiotensin converting enzyme inhibitors had not been studied previously in such patients. The present study indicates that captopril may reduce the angina threshold. The reduction in coronary perfusion pressure appears to offset the potential beneficial effects on myocardial oxygen consumption of the reduction in preload and afterload. However, the frequency of ventricular arrhythmias was also reduced in this study.

Finally an attempt was made to determine if angiotensin-converting enzyme inhibitors had had a beneficial effect on prognosis in patients with heart failure. This was an open non-randomised evaluation. Computer modelling was used to try and correct for differences in the distribution of

adverse prognostic factors between those receiving an angiotensin-converting enzyme inhibitor and those not. A non-significant trend to improved prognosis in those receiving captopril or enalapril was noted. However, there was an excess of vascular deaths in the group treated with an angiotensin-converting enzyme inhibitor, but small numbers make these findings of uncertain significance.

Angiotensin-converting enzyme inhibitors are a new modality for the treatment of chronic heart failure. The work presented in this thesis has helped establish their usefulness and limitations, and demonstrated that they are more than mere vasodilator agents. The reason for their efficacy remains to be established. Perhaps it is because they induce haemodynamic tolerance infrequently. However, correction of intra-cellular electrolyte disturbances and autonomic dysfunction could be at least as important.

PART THREE DISCUSSION AND CONCLUSIONS

CHAPTER 21: NEUROENDOCRINE ACTIVATION IN HEART FAILURE

RENIN AND ANGIOTENSIN II

In the absence opf an angiotensin converting enzyme inhibitor, renin and angiotensin II are closely related. According to our studies, approximately two-thirds of patients will have resting renin-angiotensin system activity above the normal range for our laboratory, while of 84 patients tested, only one had a suppressed plasma renin. Furthermore, the group of patients who exhibited plasma renin within the laboratory "normal" limits still had a mean plasma active renin concentration greater than that for a matched group of normal subjects. There is little doubt that diuretics play a major role in maintaining elevated plasma renin and angiotensin II in heart failure. However, in another sense, diuretics may reveal the underlying activity of systems that otherwise would be suppressed by the fluid overload that occurred due to the heart failure itself. Thus, the diuretic-treated patient may resemble more closely patients who are actively developing heart failure. In patients with untreated heart failure who achieve a compensated state without resort to diuretics, neuroendocrine activity, especially the renin-angiotensin system, may not be increased.

Patients with an activated renin-angiotensin system are characterised by lower mean arterial pressure, lower serum sodium and potassium concentrations, and a more activated sympathetic nervous system. Though there was a trend to more severe heart failure, as assessed by functional class, exercise performance, and diuretic dose, these were not significantly different between those with and without an activated renin-angiotensin system.

Examining the problem in a different way, regarding, perhaps more appropriately, the renin-angiotensin activation as a continuous variable, multiple regression analysis revealed 3 variables which carried independent predictive value for plasma active renin concentrations (Chapter 11). Plasma active renin varied linearly and directly with plasma noradrenaline, inversely with serum potassium concentration, and inversely with mean arterial pressure. These three values accounted for 75% of the variation in plasma renin (r^2 value). Although serum sodium was fairly closely related to plasma renin concentration, on multiple regression analysis this could be displaced by arterial pressure and potassium. However, it is not clear if these relationships are causal or merely associated. The relationship between plasma noradrenaline and renin is to be expected. As described in Chapter 2, the juxtaglomerular apparatus is richly innervated by sympathetic nerve fibres and increased sympathetic nerve activity may release renin directly. Sympathetically-mediated constriction of the

afferent arteriole may also contribute to an indirect increase in renin secretion.

The relationship between serum potassium concentration and plasma renin may be an equally complex interaction. In animal experiments, when potassium is infused into the afferent arteriole, plasma renin is suppressed. (Chapter 2) A low serum potassium in our patients could have stimulated plasma renin or at least had a facilitatory effect on activation by other stimuli. Other researchers have also found that potassium depletion is poorly related to diuretic therapy in heart failure but is strongly related to plasma aldosterone.[756] An activated renin-angiotensin system is therefore likely to lead to hypokalaemia. There is potential within this system for positive feedback,, with hypokalaemia causing further activation of the renin-angiotensin system and aldosterone, which itself will cause further hypokalaemia. However, hypokalaemia tends to reduce aldosterone secretion.[757]

A low mean arterial pressure will activate the renin-angiotensin system, not only directly by reducing renal perfusion pressure but also indirectly, by activating the sympathetic nervous system through baroreceptors in the carotid and aortic arches.

The kidney responds predominantly not to the serum sodium concentration but to the sodium composition of the early

distal tubular fluid, as sensed at the macula densa. In heart failure, of course, the composition of renal tubular fluid varies enormously in relationship to the diuretic dose. For instance, a hyponatraemic patient with heart failure under basal conditions will produce a small volume of highly urea-concentrated but salt-poor urine. The amount of sodium at the macula densa is likely to be small and this should activate the renin-angiotensin system. However, when the patient is given a diuretic much larger volumes of urine of low urea concentration but high sodium content are produced. This should inactivate the renin-angiotensin system but, in contrast, further activation of the renin-angiotensin system was found under these circumstances. However, frusemide may cause renin release by other mechanisms mediated through bradykinin, prostaglandins, and the sympathetic nervous system.

It is not clear why hyponatraemia should be associated with renin-angiotensin system activation. However, serum sodium was found to be directly related to mean arterial pressure. Serum sodium concentration may be a marker for arterial hypovolaemia, with anti-diuretic hormone forming a possible link;[758] the low renal perfusion pressure and more avid water retention during the diuretic-free period then produce the association between low serum sodium and high plasma renin concentration. Alternatively, hyponatraemia may be a consequence of angiotensin II-mediated stimulation of anti-diuretic hormone, high plasma concentrations leading

to an impaired ability of the kidney to formulate a hypotonic urine. Loss of the renal medullary concentration gradient, a possible consequence of raised proximal tubular reabsorption in the very low distal tubular flow, markedly reduced flow in the vasa recta as renal blood flow declines, or the effects of loop diuretics on the ascending limb of the loop of Henle and medullary core gradient, may all lead to an impaired ability of the kidney to form a dilute urine.

The only patient in whom plasma active renin concentration was not elevated also exhibited plasma noradrenaline levels which were only mildly elevated. This patient was receiving 200 mg frusemide/day, which was above the mean dose for the other patients in the study. The patient had a normal serum sodium and had essential hypertension. During exercise, he failed to activate the plasma renin-angiotensin system, although plasma noradrenaline rose appropriately. Acute challenge with frusemide also failed to cause a rise in plasma renin. Addition of enalapril in doses of up to 40 mg/day also failed to increase the plasma concentrations of active renin. He therefore appeared to have a totally inactivated renin-angiotensin system. This individual nonetheless showed apparent improvement during controlled studies of enalapril for his heart failure, and his blood pressure also fell during treatment with enalapril.

Although caution should be exercised in interpreting data

from one patient, it does emphasize the fact that renin-angiotensin system activation is not necessarily activated by diuretic therapy. This patient was not on potassium-sparing diuretics or potassium supplements, and, despite a large dose of frusemide, was not hypokalaemic, indicating the importance of the renin- angiotensin system in inducing hypokalaemia. Lastly, it suggests that the hypotensive and beneficial clinical effects of enalapril are not entirely mediated by the renin-angiotensin system, at least not as reflected in the plasma.

ALDOSTERONE

Aldosterone is secreted by the adrenal cortex and seems largely regulated by the concentration of angiotensin II, ACTH, and the concentration of sodium and potassium in the plasma. We found a close relationship between angiotensin II and aldosterone (Chapter 16), and this is likely to be the main stimulus to aldosterone secretion in heart failure. Although sodium may have direct effects on aldosterone secretion, quite large changes are necessary to produce any effect, and this seems unlikely to be of great importance. In heart failure, serum potassium is low and this should lead to a decrease in aldosterone secretion, an effect which is obviously overcome by angiotensin II. Adrenocorticotrophic hormone is probably not of great importance in regulating aldosterone in heart failure, although we have not personally examined this question. Adrenocorticotrophic hormone stimulation of aldosterone is

transient and not maintained with continued administration of ACTH. Atrial natriuretic peptide also appears to inhibit aldosterone secretion but we did not examine this in the present studies.[759] However, this effect does not appear to be of major importance in patients with heart failure.[760] Reduced catabolism of aldosterone due to impaired hepatic function may also contribute to increased plasma concentrations. [761,762]

THE SYMPATHETIC NERVOUS SYSTEM

Compared to normal age- and sex-matched controls, patients with heart failure have elevated levels of plasma noradrenaline and adrenaline. Though there is still some controversy over the source of venous catecholamines in heart failure, nonetheless they appear to reflect overall sympathetic activity fairly well.

In the 84 patients in whom we measured plasma noradrenaline under basal conditions, plasma noradrenaline was most closely related to plasma renin concentration and severity of heart failure as assessed by NYHA classification. This explained 58% of the variability in plasma noradrenaline (r^2 value). If plasma renin concentration is excluded from the analysis then the single strongest predictor of plasma noradrenaline was the mean arterial pressure. A low arterial pressure therefore which is also associated with a poor prognosis in heart failure was associated with high levels of sympathetic activity.

The stimulus to increased sympathetic activity in heart failure has not been entirely elucidated. The above findings certainly support a role for baroreceptors in the carotid and aortic arches that are influenced by changes in the arterial pressure. These high pressure resistance sites appear to be working in a physiologically normal direction (that is, a loss of effective circulating volume leads to a tendency for cardiac output and blood pressure to decline, precipitating, in turn, fluid retention and vasoconstriction to restore blood pressure). However, arterial baro-receptor activity may be more closely related to transmural arterial tension, rather than to the arterial pressure itself. The variability in arterial distensibility and in the arterial cross- sectional diameter, which, according to Laplace's law, would also markedly influence arterial transmural tension in heart failure, may account for the fact that there was not a better relationship between arterial pressure and plasma noradrenaline levels.

The increase in circulating plasma noradrenaline in heart failure seems largely derived from the cardiac and renal circulations, while reduced renal clearance of plasma noradrenaline will also elevate plasma levels.

ANTI-DIURETIC HORMONE

Two of the effects of anti-diuretic hormone on the kidney in heart failure should be to produce a small volume of urine of high urea concentration. This is exactly what is

found in the urine of patients with heart failure when diuretics are withheld.

In addition to its important role in producing an anti-diuresis in the diuretic-free phase in cardiac failure, anti-diuretic hormone may also be a potent vasoconstrictor. However, when vasopressin antagonists have been given to patients with heart failure, little haemodynamic response is observed generally, although occasionally acute hypotension may occur.

It is of some interest that during acute severe hypotension induced by a first dose of an angiotensin- converting enzyme inhibitor, we observed paralysis of both the renin-angiotensin system and the sympathetic nervous system, but adrenaline and anti-diuretic hormone both increased. Anti-diuretic hormone may be of greater haemodynamic significance during converting enzyme inhibition, and perhaps also in those patients who have a markedly low plasma osmolality.

We found elevated levels of anti-diuretic hormone in patients with heart failure, compared to normal subjects. Normally, anti-diuretic hormone is strongly influenced by the plasma osmolality. As plasma osmolality falls, anti-diuretic hormone should be suppressed. However, in heart failure, where plasma osmolality is generally low, the anti-diuretic hormone levels are elevated, indicating

a breakdown in the normal relationship.[763] Angiotensin II may stimulate anti-diuretic hormone secretion, and a strong correlation between the two was found in our studies of patients with heart failure who were not receiving ACE inhibitors. It is possible that angiotensin II might lower the osmotic stimulus threshold for anti-diuretic hormone release or stimulate its release by centrally-mediated mechanisms.[764] However, the relationship may be even more complex. Although plasma concentrations of anti-diuretic hormone generally declined during chronic ACE inhibitor therapy, anti-diuretic hormone eventually rose in those patients who developed low arterial pressures and pre-renal uraemia, despite the fact that angiotensin II had been markedly suppressed. Thus, a reduction in arterial baro-receptor activity may release anti-diuretic hormone from tonic inhibition.[765] A low arterial pressure may therefore be a common stimulus to angiotensin II and anti-diuretic hormone secretion in heart failure, or may sensitise anti-diuretic hormone release to angiotensin II.

A fall in right atrial pressure could stimulate anti-diuretic hormone release, though this only pertains to patients with heart failure over-treated with diuretics. However, there is accumulating evidence that afferent and/or efferent pathways in atrial reflexes are reduced in cardiac failure. Impaired afferent or efferent expression of the effects of raised atrial pressure on suppression of anti-diuretic hormone secretion could also be important.[766]

ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide is elevated in patients with cardiac failure. Concentrations vary directly with mean right atrial pressure and are also weakly related to plasma active renin concentration in patients with heart failure.[767]

This concurs with others studies, suggesting a close relationship between transmural atrial, in particular right atrial, pressures. Atrial natriuretic peptide has many effects, including the ability to relax vascular smooth muscle, inhibit vasoconstriction induced by angiotensin II and noradrenaline, and reduce secretion of renin, aldosterone and anti-diuretic hormone.[759] However, as the name suggests, its primary physiological function appears to be to promote natriuresis and diuresis as right atrial pressure rises. This potentially useful reflex in cardiac failure unfortunately appears to be impaired.[760] Although markedly elevated levels of atrial natriuretic peptide are observed, clearly a sufficient diuresis does not ensue. It is not yet clear if the relationship between plasma concentrations of atrial natriuretic peptide and atrial pressure in heart failure is different from what might be observed in a normal heart. Studies in animals suggest that the raised levels of atrial natriuretic peptide are still having some effect. Injection of antibodies to atrial natriuretic peptide leads to an anti-diuresis.[768] The relative resistance of the kidney in heart failure to the effects of atrial natriuretic peptide could be due to

receptor down- regulation, antagonism by the renin-angiotensin or sympathetic nervous system, or due to the relatively low arterial perfusion pressure.

NEUROENDOCRINE EFFECTS OF DIURETICS IN HEART FAILURE

Some investigators have suggested that the renin-angiotensin system is not activated in untreated heart failure, though such studies have not included comparison with normal controls. Administration of diuretics to such patients results in a decline in plasma noradrenaline and an increase in plasma renin.

Studies on the effects of intravenously-administered frusemide to patients with heart failure have also demonstrated acute increases in renin, noradrenaline, and anti-diuretic hormone. This was accompanied surprisingly by a rise in atrial pressures and an increase in vascular resistance. All these effects had disappeared by 4 hours in one study, rather surprising in view of the associated diuresis and volume contraction.[769,770]

Our studies were carried out in patients with chronic stable heart failure receiving long-term diuretic therapy. A further dose of oral frusemide led to further increases in plasma concentrations of renin, angiotensin II, aldosterone, anti-diuretic hormone, and noradrenaline. This was attended by an acute fall in plasma concentrations of potassium and sodium.

Frusemide can stimulate plasma renin release acutely by a variety of mechanisms. Sympathetic activation by diuretics has been previously described in hypertension and is probably due to volume depletion. [771] The late activation of renin is probably a sympathetically- mediated phenomenon. The rise in plasma anti-diuretic hormone may be secondary to the increase in angiotensin II or to a fall in plasma osmolality, as reflected by the fall in sodium and potassium. The fall in sodium and potassium may also play a role in the release of renin in response to the diuretic.

NEUROENDOCRINE RESPONSE TO STANDING

We compared the neuroendocrine responses to standing in normal subjects and patients with heart failure. We observed no further activation of the renin-angiotensin-aldosterone system or anti-diuretic hormone in patients with heart failure, while a small increase only in renin and aldosterone occurred in normal controls. In contrast, plasma noradrenaline increased distinctly in normal subjects but failed to do so in patients with heart failure. This is in accordance with other studies which have suggested that basal sympathetic activity is increased in heart failure but that sympathetic responses are blunted. Heart rate, another index of sympathetic reflex activity, failed to rise in a normal fashion on assumption of the erect posture in patients with heart failure. Other investigators have found that upright posture activates the

renin-angiotensin system but most of these studies have been performed with a tilt table where reflex activation may be more intense than that due to standing.[772]

Patients with heart failure may have a blunted increase in sympathetic activity during standing due to their relatively high venous and arterial tone. Cardiac output normally falls on standing up as venous pooling occurs in the legs. A potential fall in blood pressure is averted by baroreflex activation, an increase in sympathetic activity, and peripheral vasoconstriction. In patients with heart failure, high atrial pressures and venous constriction combine to prevent cardiac output falling in the upright position, preventing the need for a reflex increase in sympathetic activity. The failure of sympathetic activity to increase may in turn account for the lack of an increase in renin during standing.

An alternative explanation is that the sympathetic nerve terminal in heart failure may suffer from one or more biochemical defects, leading to decreased reflex responsiveness and a reduction in noradrenaline release to the plasma.

NEUROENDOCRINE RESPONSES TO EXERCISE

We compared the clinical and neuroendocrine responses of a maximal exercise test in patients with heart failure to that of normal subjects exercised to the same absolute

workload and to their maximum exercise capacity. The maximum exercise protocol for the normal subjects had been specifically designed so that they exercised for a similar time to the patients with heart failure, thus preventing effects due to the duration of exercise.

Exercise provoked an approximately 30% increase in mean plasma concentrations of renin, angiotensin II and aldosterone, while concentrations of noradrenaline and anti-diuretic hormone more than doubled during a maximum exercise test in the patients with heart failure.

The neuroendocrine response to exercise in patients with heart failure must be interpreted with extreme caution. Under basal conditions, neuroendocrine activation is greater in patients with heart failure than in normal controls. During exercise at the same workload, activation of the renin-angiotensin system and anti- diuretic hormone are more intense in subjects with heart failure. Sympathetic activity, as reflected by plasma noradrenaline, is still less intense in normal subjects than that seen in patients with heart failure but the relative increase is as great in normal subjects. Heart rate at the same workload is higher in patients with heart failure, an indirect index of sympathetic activity, as is the absolute increase from rest. Comparing **maximum** exertion in normal subjects and controls (exercised for the same duration, but different intensity), normal subjects had a much more intense

activation of all neuroendocrine systems compared to patients with heart failure. Absolute plasma levels of noradrenaline, adrenaline, and anti-diuretic hormone were higher at maximum exercise in normal subjects. Although absolute levels of renin-angiotensin system activity were lower in normal subjects at maximum exercise, the percentage increase was greater than that found in patients with heart failure.

Activation of the sympathetic nervous system during exercise is partly centrally mediated, increases in sympathetic activity occurring in anticipation of exercise but also probably dependent on input from mechano-receptors in joints and muscles. Increased circulating noradrenaline during exercise seems largely derived from exercising muscles, perhaps associated with beta-$_2$receptor-mediated peripheral vasodilation. Cardiac and renal noradrenaline release both increase during exercise and this is enhanced in heart failure. [773,774] Transient reductions in arterial oxygen tension during exercise would also enhance sympathetic function at a given level of baro-receptor activity.[775] Finally, the heart is richly supplied with afferent sympathetic fibres. Alterations in filling pressures may reflexly stimulate sympathetic activity.

Patients with heart failure had a sustained increase in plasma noradrenaline after exercise when compared to normal subjects. This may have important implications for

post-exercise arrhythmias and post-exercise hypokalaemia.

The increase in renin during exercise could be due to activation of renal sympathetic efferents. However, although plasma noradrenaline increased by a broadly similar amount in patients with heart failure and normal controls exercised to the same workload, plasma renin only increased in those with heart failure. An alternative explanation is that renal ischaemia develops during maximal exercise as blood is diverted to exercising muscle. This would explain why renin increased in both groups during intense exercise. A reduction in tubular sodium delivery during exercise could also have stimulated renin secretion.

CHAPTER 22: THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS ON NEUROENDOCRINE ACTIVATION IN HEART FAILURE

Angiotensin-converting enzyme inhibitors have complex haemodynamic and metabolic effects, not only because they inhibit the formation of angiotensin II which interferes with many other neuroendocrine systems but also because they inhibit other enzymes such as bradykininase, and may affect prostaglandin metabolism.

PLASMA ACTIVE RENIN CONCENTRATION

Freed from the negative feedback of angiotensin II, plasma active renin concentration rises. Even though large amounts of renin may appear in the circulation, this has no active role as the sole effect of this enzyme is to convert angiotensinogen to angiotensin I. The amount by which renin increases is highly variable, and may be useful as an indicator of the underlying stimulation to renin excretion in the absence of negative feedback from angiotensin II. Some authors have suggested that the increase in plasma renin in response to an ACE inhibitor predicts a good clinical response.[776]

ANGIOTENSINOGEN

Angiotensinogen formed in the liver is under the positive feedback influence of angiotensin II. Chronic reduction in angiotensin II leads to a decreased synthesis of the substrate for renin.

ANGIOTENSIN I

After converting enzyme inhibition, angiotensin I accumulates, but this molecule probably has little biological effect. However, as angiotensin I accumulates, even a small amount of free converting enzyme may cause further rapid synthesis of angiotensin II. Large amounts of angiotensin I in the circulation also cause problems as they may cross-react with the angiotensin II assay, giving falsely high concentrations of angiotensin II. Formulae should either be adjusted to take this into account, depending of the specificity of the antibody in the radio-immunoassay. Alternatively, the angiotensin I and II may be separated using high performance liquid chromatography. (See Methods)

ANGIOTENSIN-CONVERTING ENZYME

In response to blockade of the converting enzyme, total levels of the enzyme go up. Eighty per cent or more occupation of the enzyme's binding sites by an inhibitor is required before any suppression of angiotensin II takes place. These considerations must be kept in mind when dosing with ACE inhibitors. However, it should be mentioned that some authors have found that low doses of converting enzyme inhibitors, which probably suppress angiotensin II for a few hours per day only may still have beneficial effects on patients with cardiac failure. These studies were not well controlled, and await confirmation.[777]

ANGIOTENSIN II

Angiotensin II is, of course, suppressed after administration of a converting enzyme inhibitor. In our long-term study on captopril we took blood samples 10 hours after the last dose of chronically administered drug. It was apparent that there was some breakthrough, though incomplete, in converting enzyme inhibition. In the study on enalapril the samples which were taken under basal conditions were 24 hours after the last dose of enalapril, and again there appeared to be some breakthrough from converting enzyme inhibition, although this was to a much lesser extent that in the study on captopril. Further angiotensin II suppression occurred 4 hours after the next dose of enalapril. Increases in angiotensin I and the converting enzyme itself during chronic ACE inhibition make it likely that larger doses of inhibitors are required to suppress angiotensin II completely during long-term studies.

ALDOSTERONE

Initially, on introduction of a converting enzyme inhibitor, aldosterone falls rapidly to low levels. However, after several months of treatment, aldosterone levels rise, although not back to baseline. The associated rise in serum potassium with chronic therapy could stimulate aldosterone release and is probably responsible. However, during the enalapril study when a further dose of enalapril was given, a further fall in aldosterone levels

was observed. This apparent marked sensitivity of aldosterone to angiotensin II could be explained by a sensitising role of potassium or by an up-regulation of angiotensin II receptors in response to the generally low prevailing levels of angiotensin II. This rise in aldosterone during chronic converting enzyme inhibition should probably be viewed as a useful safety valve, preventing excessive accumulation of potassium and dangerous hyperkalaemia. Certainly, hyperkalaemia is commonly noted when converting enzyme inhibitors and aldosterone antagonists are used together.

THE SYMPATHETIC NERVOUS SYSTEMS

In both acute and chronic studies with converting enzyme inhibitors, plasma noradrenaline concentrations fell. Less marked effects on plasma adrenaline were noted, though the apparent lack of effect may be due to the difficulties in measuring plasma adrenaline accurately. The reasons for the decline in sympathetic activity may be several. An improvement in cardiac failure would reduce the stimulus to the sympathetic nervous system. Alternatively, angiotensin II has been shown to have direct stimulatory effects on sympathetic nerve terminals. Changes in the composition and properties of the arterial wall could also account for some of the long-term changes in sympathetic activation by altering the relationship between arterial pressure and baroreceptor activation.

The reduction in sympathetic activity is all the more surprising as it occurs in the setting of a fall in mean arterial pressure, apparently one of the major stimuli to the increase in sympathetic activity in heart failure.

It is remarkable that even when severe hypotension occurred after initial doses of a converting enzyme inhibitor, plasma noradrenaline failed to rise, although plasma adrenaline still responded. It is possible that this paralysis of sympathetic nerve function was an effect of angiotensin II suppression. However, it appears that sympathetic paralysis may be a general feature of patients who faint. Adrenal medullary responses may be mediated through parasympathetic efferents and therefore may respond differently.

ANTI-DIURETIC HORMONE

As expected, anti-diuretic hormone, which may be largely under the influence of angiotensin II in patients with heart failure, was reduced during converting enzyme inhibition. Although anti-diuretic hormone levels generally fell during converting enzyme inhibition, increases were seen in patients who developed hypotension, whether acute or chronic. In those patients who developed very low blood pressures during long-term converting enzyme inhibition, the increase in anti-diuretic hormone was associated with hyponatraemia.

Released from the negative feedback of angiotensin II, the already elevated concentrations of plasma active renin demonstrate an exaggerated rise after frusemide. The rise in angiotensin II and aldosterone normally observed after administration of frusemide was inhibited. Although the rise in plasma noradrenaline after the diuretic was suppressed, the rise in anti- diuretic hormone was not.

It should be noted that in a short-term interactive study (Chapter 16) that patients had gained weight. There was also evidence of blood volume expansion and reduced urine volumes in response to diuretic. The suppression of the rise in plasma noradrenaline under these circumstances could be due not only to the loss of the direct effects of angiotensin II on the sympathetic nerve terminal but also a failure of blood volume to contract sufficiently to act as an afferent stimulus to the sympathetic nervous system. However, data from longer term studies (Chapter 15) also show a failure of plasma noradrenaline to increase after frusemide, despite the fact that body weight was similar before and after converting enzyme inhibition. Although plasma anti-diuretic hormone was reduced by enalapril in the absence of a diuretic, the rise after the administration of frusemide was not. This was reflected by a reduction in free water clearance when enalapril and

frusemide were administered together. The stimulus to the increase in anti-diuretic hormone is not clear, but may well have been the reduction in blood pressure with the combination of diuretic and ACE inhibitor. Anti- diuretic hormone increases during hypotension in otherwise normal subjects.[778] It also increases in response to syncope induced by the administration of an ACE inhibitor, when other neuroendocrine systems appear paralysed. We also noted that in those subjects who developed postural hypotension and hyponatraemia during chronic converting enzyme inhibition anti-diuretic hormone levels increased, unlike their counterparts without this problem. Anti-diuretic hormone may be a vasoconstrictor under these circumstances providing some protection from severe falls in blood pressure.

THE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS ON THE NEUROENDOCRINE RESPONSE TO CHANGES IN POSTURE

The rise in plasma renin during standing was slightly, though not markedly, enhanced by chronic enalapril therapy. The rise in plasma angiotensin II was completely suppressed, as was the rise in plasma aldosterone. The reflex increase in plasma noradrenaline in response to standing was restored in patients with heart failure during chronic treatment with enalapril and was comparable to that seen in normal subjects. Thus, the reductions in plasma noradrenaline after ACE inhibition observed in the supine position were lost on standing.

The reasons for the restoration of the increase in noradrenaline on standing have not been fully elucidated. Sympathetic responses could have returned to normal as heart failure improved. The reduction in angiotensin II may have induced changes in sympathetic nerve terminals, allowing noradrenaline stores to replete. However, as blood pressure fell more during standing after enalapril, the stimulus to the sympathetic nervous system may have been greater. This increase in reflex sympathetic responsiveness was reflected by a significant rise in heart rate on standing after converting enzyme inhibitor, which was not seen in patients with heart failure prior to this.

The increase in anti-diuretic hormone during standing was variable, but those patients who had the greatest postural fall in blood pressure showed a prominent rise in anti-diuretic hormone. Thus, the fall in blood pressure again is the most likely stimulus to anti- diuretic hormone secretion on standing.

THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR ON NEUROENDOCRINE RESPONSES TO EXERCISE.

During exercise, plasma renin rose markedly during treatment with enalapril, presumably because of the loss of angiotensin II feedback. Even during maximal converting

enzyme inhibition, there was some slight increase in angiotensin II during exercise which did achieve statistical significance. Although pre-exercise aldosterone was suppressed, the relative rise in aldosterone during exercise was identical on enalapril compared to placebo. This suggests that other factors such as the rise in serum potassium with exercise may be important in controlling aldosterone secretion under these circumstances. The rise in plasma noradrenaline, in heart rate, and in anti-diuretic hormone during exercise appeared unaffected by converting enzyme inhibitors. Others have suggested that ACE inhibitors may reduce cardiac sympathetic activation during exercise and reduce plasma noradrenaline at a given workload.[779-781] The present study could have missed a small effect as patients were all exercised to their maximum capacity. Enalapril improved exercise performance which could have introduced a consistent bias in our results.

During long-term enalapril therapy, plasma noradrenaline levels declined more rapidly after exercise when compared to the placebo period. This is much more akin to the catecholamine response observed in normal subjects. It may account for the prevention of post- exercise hypokalaemia observed during enalapril therapy and may also have contributed to a reduction in arrhythmias observed with chronic enalapril therapy.

ATRIAL NATRIURETIC PEPTIDE

Assays for atrial natriuretic peptide were not available at the outset of most of the studies presented here. In one small study acute administration of an ACE inhibitor caused a fall in plasma levels, while atrial natriuretic peptide levels rose over the subsequent week as weight gain occurred in response to the introduction of an ACE inhibitor. This is consistent with the effects of ACE inhibitors on atrial pressures. This reduction in atrial natriuretic peptide is one mechanism which might cause fluid retention immediately after giving an ACE inhibitor. Longer-term studies have suggested that ACE inhibitors may reset the relationship between atrial natriuretic peptide and atrial pressure such that, for a given pressure, a higher plasma level of peptide is present.[782]

SUMMARY

In this section we have outlined not only the neuroendocrine responses of patients with chronically treated cardiac failure but have also defined the response of these systems to a variety of everyday stimuli. Angiotensin-converting enzyme inhibitors appear effective in suppressing angiotensin II in all these situations. Aldosterone is generally suppressed, except during exercise, perhaps indicating an important role for potassium, which also increases during exercise, as a stimulus for aldosterone secretion under these

circumstances. The decline in sympathetic nervous system activity is consistent between studies, though whether this is due to an improvement in the heart failure or a specific effect of reducing angiotensin II is unclear. Activation of the sympathetic nervous system during standing is blunted in patients with heart failure but this is reversed by ACE inhibition. The increase in sympathetic nervous activation during exercise appears unaffected by angiotensin converting enzyme inhibitors in our studies. However, increased sympathetic nervous activity due to the administration of diuretics is blocked.

Anti-diuretic hormone appears suppressed by converting enzyme inhibitors with the patient in the supine position under "basal" conditions, but appears to rise in response to diuretics and exercise.

CHAPTER 23: METABOLIC CHANGES IN CARDIAC FAILURE

INTRODUCTION

This chapter will concentrate on the effects of heart failure on serum electrolytes and total body elemental composition.

Serum Sodium

Comparing patients with heart failure to normal controls or patients with hypertension, patients with heart failure had a lower serum sodium. Hyponatraemia was confined to those patients with an elevated plasma renin. Patients who did not have an elevated basal plasma renin had exactly the same mean serum sodium as hypertensive patients and normal controls. The link between hyponatraemia and an elevated plasma renin is complex, and it is unclear which of these is the dependent response. The effects of diuretic agents on renin release by the juxtamedullary apparatus may be important.[785,786] The effect of sodium at the macula densa must be complex as distal tubular delivery of sodium must vary widely before and after dosing with diuretics while plasma renin remains elevated in both circumstances. Anti-diuretic hormone, which may be largely under the control of angiotensin II in this setting, could have promoted dilutional hyponatraemia. Thus, activation of the renin-angiotensin system may be the primary event in the induction of hyponatraemia.

Although the use of diuretics probably contributes greatly to the development of hyponatraemia, the relationship between diuretic dose and plasma renin or hyponatraemia was poor. This may reflect differences between patients in the absorption or renal effects of diuretics. Diuretics may induce hyponatraemia by impairing the ability of the kidney to produce a hypotonic urine, that is, they produce, directly or indirectly, a greater natriuresis than aquaresis. Other potential mechanisms that may induce hyponatraemia in heart failure include altered renal haemodynamics, enhanced thirst, or total body potassium depletion.[790,791] Interference with renal prostaglandin synthesis greatly increases the risk of developing hyponatraemia in patients with heart failure[792,793]

In addition to the strong link between plasma renin and serum sodium, hyponatraemic patients also had higher levels of angiotensin II, aldosterone, noradrenaline and anti-diuretic hormone. We found only a weak correlation between serum sodium levels and serum urea and creatinine, suggesting that hyponatraemia is not merely caused by a decline in renal function in heart failure. Serum sodium was strongly correlated with serum chloride, again indicating some deficiency in function at the level of the loop of Henle, probably diuretic- induced. Serum sodium and potassium also correlate fairly well in patients not receiving potassium-sparing diuretics. Again, activation of the renin-angiotensin- aldosterone system and anti-diuretic

hormone may constitute the common link.

Comparing subjects with heart failure to those with hypertension, patients with heart failure have an expanded extracellular fluid volume and increased total body sodium. This confirms that hyponatraemia under such circumstances is due to excessive water retention rather than sodium depletion.

We found that serum sodium tended to fall acutely after frusemide administration in chronically diuresed patients, there being a one millimole fall in serum sodium 4 hours after oral dosing. This was associated with further activation of neuroendocrine systems. We found no effect of posture but exercise caused a small but significant increase in serum sodium concentration, despite further activation of neuroendocrine systems.

Serum Potassium

In comparison to subjects with hypertension and normal controls, patients with treated heart failure who were not on potassium-sparing diuretics (though some were receiving potassium supplements), had markedly lower serum concentrations of potassium. Potassium depletion was associated with markedly elevated levels of plasma renin and aldosterone but was poorly related to the dose of frusemide. Patients who were hypokalaemic were more likely to be receiving potassium supplements which therefore

appeared to have remarkably little effect on serum potassium in this setting. Diuretic agents are the likely cause of hypokalaemia in our patients but the relationship is not direct; it is mediated through aldosterone. Only those patients who activate the renin-angiotensin-aldosterone system develop hypokalaemia. It is possible that increased sympathetic activity could have driven potassium from the extracellular to the intracellular compartment in addition. Indeed, despite a reduction in total body potassium, intracellular potassium was relatively preserved compared to serum potassium in patients with heart failure.

Concentrations of serum bicarbonate were higher in patients with heart failure, as might be expected in the presence of hypokalaemia, but bicarbonate concentrations were similar in normal and high renin subgroups, despite significant differences in serum and total body potassium. A long-term increase in serum bicarbonate and alkalosis may be less important in the regulation of the intra-/extracellular potassium ratio in treated heart failure, though it may have a short-term regulatory role.

In response to orally administered diuretic, we noted a fall in serum potassium of 0.3-0.4 mmol/l over the subsequent 2-4 hours. This was associated with increased renin-angiotensin system and sympathetic nervous activity, both of which may have contributed to this. Though posture

had no significant effect on serum potassium, exercise resulted in a rise in serum potassium but this was less than in normal subjects either exercising at the same workload or at maximal exercise. However, marked falls in serum potassium were seen in the post-exercise period in patients with heart failure. This was associated with a prolonged period of elevated sympathetic activity.

These acute changes in serum potassium activity undoubtedly represent shifts between the intra- and extracellular space. They could readily be accounted for by the noted variations in sympathetic activity. Alternatively, intracellular acidosis developing readily in the patient with heart failure due to the reduced skeletal muscle blood flow could also have altered the exchange of hydrogen and potassium ions across the cell membrane.

Intracellular potassium stores are depleted in heart failure. This may limit the rise in serum potassium during exercise, thereby exaggerating post-exercise hypokalaemia. Additionally, depleted intracellular stores of potassium may accept more avidly extracellular potassium under the influence of the sympathetic nervous system.

Serum Bicarbonate

This has been discussed above briefly. Patients with heart failure appear to have a mild extracellular alkalosis, perhaps representing a deficiency in the hydrogen-potassium

exchange across the cell membrane, or changes in the sodium and hydrogen ion exchange in the distal convoluted tubule.[794]

Serum Chloride

The chloride ion may well be the primary ion on which frusemide has its action in the loop of Henle. Sodium is excreted in conjunction with it to maintain cation- anion balance. The two were closely correlated throughout our studies.

Serum Calcium and Phosphate

We did not carry out a controlled comparison of these electrolytes between normal subjects and subjects with heart failure. However, the values did not seem to differ from the normal laboratory range.

Glucose

Although overt diabetes mellitus was excluded from many of our studies, it became apparent that impaired glucose metabolism was common. Several patients developed overt diabetes mellitus during the course of the study. Although the age group studied is one in which a relative high prevalence of glucose intolerance would be expected, this was probably exacerbated by diuretic therapy. Reports of ACE inhibitors causing increased insulin sensitivity indicates that the renin-angiotensin system may play a role in induction of glucose intolerance.[795]

Serum Urate

Serum urate was generally elevated beyond the normal range, although we did no direct comparative studies. This is a further side-effect of diuretic therapy.

Several patients experienced gout during the course of these studies. Allopurinol may readily prevent this problem but should probably be prescribed in reduced doses in view of the impaired renal function in patients with heart failure. It should be noted that adverse responses to the combination of allopurinol and ACE inhibitors have been recorded, patients developing eosinophilia.

TOTAL BODY ELEMENTAL COMPOSITION

Total Body Sodium

Total body sodium was elevated in patients with cardiac failure, despite the fact that the patients specifically studied for elemental analysis were oedema-free. Only a small part of this sodium excess could be accounted for by an increase in sodium in the extracellular space, as derived from measurements of the extracellular fluid volume and serum sodium concentration. This suggests that either sodium must be trapped in the intracellular space or in bone matrix. However, when we measured total body calcium and phosphorus, the best indices of bone mass, the trend towards an excess in patients with heart failure was not significant. Thus, it is likely that there is an excess of intracellular sodium in patients with cardiac failure. This

may represent a defect in sodium-potassium ATPase due to impaired nutritional supply, particularly to skeletal muscle, or due to neuroendocrine changes, or to digoxin.[796]

In myocardial tissue, an excess of intracellular sodium may potentiate the inotropic effect of calcium. Indeed, this is one of the effects of digoxin.[797] An increase in vascular wall sodium may also contribute to vascular stiffness in heart failure and may account for some of the delayed response to converting enzyme inhibitors.

Total body sodium was elevated in patients with heart failure, both with and without elevated plasma renin levels, though it tended to be highest in those with suppressed plasma renin.

Serum sodium and total body sodium did not correlate well. This may be in part due to the large and variable amount of sodium present in bone.

Total Body Potassium

Our present studies clearly show that total body potassium depletion does occur in patients with heart failure treated with digoxin and diuretics. Others have argued that potassium depletion in such patients is due to cachexia and a loss of protein (nitrogen mass).[798,799] Our study demonstrates that this is not the case and in fact the tendency for higher body calcium and nitrogen suggests that

adipose tissue may be preferentially lost in subjects with heart failure with a relative preservation of lean body mass. Indeed, the percentage of body weight consisting of fat has been shown to be lower in elderly patients with heart failure than in age-matched controls.[800] James et al[799] have argued that potassium depletion in cachectic patients is due to a loss of cellular nitrogen mass with preservation of collagen nitrogen mass, and that this accounts for the fall in potassium in relation to nitrogen in wasting disease. They did not, however, specifically study patients with heart failure. Although Burkinshaw and Morgan[801] noted a fall in potassium in relation to nitrogen in heart failure, they too were unable to distinguish between relative changes in collagen and cellular nitrogen because their control groups differed markedly from the study group. Our groups were well matched for height, weight, age, and sex, and also had very similar total body nitrogen. If cell mass had been lost, nitrogen values should have fallen, even if collagen nitrogen mass was preserved. Further support for a true depletion of potassium rather than a change in cellular mass comes from the demonstration that the total body potassium deficit can be corrected without a change in total body nitrogen by the use of angiotensin-converting enzyme inhibitors, presumably by suppressing angiotensin II-mediated aldosterone secretion. However, amiloride and spironolactone have not been shown to correct long-term total body potassium deficits in patients with heart failure.[802,803]

Others have reported a poor, non-linear, relation between serum potassium and total body potassium. In our series, where diagnosis was tightly defined and treatment well documented and uniform, we found a good and apparently rectilinear relation between serum and total body potassium (expressed as a percentage of predicted normal) over the measured range. Multiple blood sampling may have improved this relationship (serum potassium was measured at least twice and on up to 5 occasions), as diurnal variation in potassium concentration as shown above is likely to be exaggerated by diuretic therapy. Total body potassium would not have been expected to respond in such a rapid manner.

Diuretic treatment, though associated with potassium depletion, is probably not the direct cause. When patients with high and patients with normal or low plasma active renin concentrations were compared, only the former were significantly potassium deplete, though the diuretic dose was very similar in the 2 groups. Even after appropriate corrections for nitrogen, the depletion of potassium in the group of patients with normal plasma renin was not significant. When the sodium-potassium ratio was examined, this was markedly increased in patients with heart failure compared to normal subjects or subjects with hypertension, being most markedly elevated in those subjects with an activated renin-angiotensin system.

Total Body Nitrogen, Calcium, and Phosphorus

Nitrogen is largely present in the protein of skeletal muscle and the viscera, tissues which are particularly rich in potassium. Our studies demonstrate that patients with heart failure have higher than expected total body nitrogen compared to predicted normal values. Patients with heart failure also tended to have higher levels than patients with hypertension, though this did not achieve statistical significance. The increase in nitrogen values was especially marked in those subjects who had normal or low plasma renin levels. It has been suggested that lean body mass declines with the onset of cardiac failure. Our study suggests that, if this is so, then the fall in either body water or adipose tissue mass is greater. This is further supported by the finding that total body calcium is above normal predicted levels, though again not statistically greater than in patients with untreated hypertension. The ratio of calcium to phosphorus was altered in patients with heart failure, perhaps reflecting an effect of diuretics on bone metabolism.[804,805] We found little difference in total body calcium or phosphorus in patients with and without an activated renin-angiotensin system.

These data suggest that the patients with heart failure may have been originally significantly heavier than normal controls or hypertensive subjects but that, with time, they had lost body mass, mostly adipose tissue, with relative preservation of skeletal muscle and bone. Cardiac cachexia

probably represents an extreme form of what we observed in this study.

Total Body Chlorine

Total body chlorine appeared slightly higher in cardiac failure with or without an activated renin-angiotensin system when compared with expected values or hypertensive patients, though this did not reach statistical significance. Chloride is largely present in the extracellular space and there is no evidence that this situation is altered in cardiac failure. As extracellular chloride concentrations are reduced in heart failure, the calculated extracellular fluid volume was increased, despite the fact that the patients studied were oedema-free. It is not clear whether a further increase in the dose of diuretic would have corrected this. Further diuresis may merely deplete the intravascular volume causing pre-renal uraemia, without correcting extracellular fluid volume overload.

Total Body Oxygen

Surprisingly, total body oxygen, which is an index of total body water, appeared to be depleted in patients with cardiac failure, both compared to hypertensive subjects and to expected values. Even when corrected for body weight, total body oxygen was still lower in the heart failure group. As extracellular water was in excess, this suggests that intracellular dehydration may be present. This could

explain some of the apparent intracellular potassium deficit. Intracellular potassium concentrations may be less reduced than the absolute amount of intracellular potassium. Likewise, loss of intracellular water may have reduced body weight in the heart failure subjects, accounting for some of the changes seen in nitrogen, calcium and phosphorus composition.

Intracellular dehydration could be an effect of diuretic therapy. Alternatively, water may have followed potassium out of the cell in order to maintain intracellular isotonicity. Total body oxygen was no different in high and low/normal renin subsets. As potassium was only deplete in the high renin subset this does suggest that this group of patients is still relatively potassium deplete.

SUMMARY

Patients with heart failure treated with diuretics have marked abnormalities, not only in the electrolyte composition of the extracellular fluid but also the intracellular environment. We have presented evidence that such patients still have an expanded extracellular space but apparently intracellular dehydration. Although I have presented evidence for both an extra- and intracellular potassium deficit in patients with heart failure, because of the evidence for intracellular dehydration, potassium concentrations may not have changed so dramatically in the whole group. Nonetheless, the evidence still suggests that

a true reduction in intracellular potassium concentrations as well as amount exists in patients with heart failure and high renin concentrations.

Oedema-free patients still appear to have sodium excess and in view of the reduction in extracellular sodium concentration and only slight increase in extracellular volume, this supports the hypothesis that an excess of intracellular sodium exists in heart failure.

I have also shown that our patients did not have a relative reduction in lean body mass and suggest that weight loss due to heart failure may be due predominantly to a reduction in body water or adiposity. The relative importance of the heart failure state itself, diuretics, and activation of the renin- angiotensin system await further study.

CHAPTER 24: METABOLIC CHANGES IN CARDIAC FAILURE: THE CONSEQUENCES OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION

Serum Sodium

In 2 well controlled studies, I have demonstrated that ACE inhibitors do not materially affect mean serum sodium in patients with heart failure. This is in contrast to some cited papers on this subject.[806,807] However, many other investigators have noted a failure of converting enzyme inhibitors to correct hyponatraemia,[808,809] and that angiotensin converting enzyme inhibitors may actually cause hyponatraemia sometimes.[810,811]

Packer et al [807] demonstrated a consistent rise in serum sodium from the 3rd - 4th day after introduction of an ACE inhibitor in a large number of patients with heart failure. However, the study was not performed in a controlled fashion.

In studies performed during the first week of converting enzyme inhibition, we have consistently shown in a population not selected on the basis of pre-existing serum sodium concentration, a tendency for serum sodium to fall. This occurred in the setting of renal sodium retention, blood volume expansion and weight gain, indicating dilutional hyponatraemia. This may have occurred in response to a fall in mean arterial pressure and an acute decline in glomerular filtration. Also, a decline in atrial

natriuretic peptide could have been responsible for sodium retention while an increase in anti-diuretic hormone may have reduced free-water clearance. In contrast, over 6-8 weeks we saw no change in mean serum sodium. However, detailed study of the patients revealed some interesting variations. Several patients who were initially hyponatraemic had this corrected with long-term enalapril. These patients tended to have a good clinical response without developing excessively low blood pressures or symptoms of postural hypotension. In contrast, another group of patients actually acquired hyponatraemia during the course of the study. These patients also showed clinical improvement with an ACE inhibitor but developed postural hypotension and more prominent increases in serum urea and creatinine. Interestingly, in these patients plasma anti-diuretic hormone actually increased during ACE inhibition, with more marked increases being seen on standing. Hyponatraemia in the setting of long- term ACE inhibition occurred without an increase in body weight or total body sodium which is in contrast to the early onset hyponatraemia.

The increase in anti-diuretic hormone is presumably in response to reductions in blood pressure in both early and late hyponatraemia. Angiotensin converting enzyme inhibitors do not appear to prevent the acute fall in serum sodium after the administration of diuretics.

Serum Potassium

Although angiotensin-converting enzyme inhibition would be expected to correct hypokalaemia, not all studies agree that serum potassium changes, although, interestingly, some of these studies do note that dangerous hyperkalaemia developed when ACE inhibitors and potassium-sparing diuretics (particularly spironolactone) were combined.[812] Our studies show no acute effects of an ACE inhibitor on serum potassium, despite marked renal potassium retention. The associated weight gain and fluid retention may account for this in part. We noted an increase in blood volume one week after instituting enalapril in our patients. However, if all the weight gain was extracellular we would have expected to observe a 5 mmol/l increase in serum potassium in the first week of therapy. Obviously, an increase in intracellular potassium must have taken place. It is not clear whether the increase in intracellular potassium reflected an increase solely in concentration or if a simultaneous increase in intracellular water took place. However, even in the early phase of ACE inhibition, the acute fall in serum potassium after diuretic administration is inhibited. This is not only associated with suppression of the renin-angiotensin system but also the sympathetic nervous system, and suggests that acute diuretic-induced hypokalaemia may be attributed to activation of one or both of these systems.

During long-term angiotensin converting enzyme inhibition,

mean serum potassium rises on average 0.5- 0.6 mmol/l. This is accompanied by a smaller increase in serum magnesium which may also be partially under the control of aldosterone. During long-term ACE inhibition, not only is basal serum potassium increased but the diuretic-induced fall in potassium is blocked and the rise in serum potassium during exercise is maintained without any exaggerated fall in serum potassium in the post-exercise period. Sympathetic activity at peak exercise was similar in patients before and after ACE inhibition, but plasma noradrenaline fell more rapidly after exercise during treatment with an ACE inhibitor. This may account for the correction of post-exercise hypokalaemia by enalapril.

Serum Bicarbonate

In conjunction with the correction of hypokalaemia, serum bicarbonate fell towards normal and this may suggest also that a relative intracellular hydrogen ion excess was corrected.

Serum Chloride

Serum chloride levels did not change with chronic ACE inhibition. On analysing subsets, chloride ion tended to follow a similar pattern to the sodium ion.

Serum Calcium

This was unaltered by converting enzyme inhibition. The effects of ACE inhibitors on ionised calcium were not specifically examined. Changes could have occurred in view of the change in serum bicarbonate.

Serum Phosphate

Serum phosphate rose consistently during chronic ACE inhibition. This probably reflects a decline in glomerular filtration rate, although the possibility that this may also reflect subtle changes in renal tubular phosphate handling cannot be excluded.

Serum Urate

We saw no effect of ACE inhibitors on serum uric acid.

Plasma Glucose

No consistent change in plasma glucose occurred during ACE inhibition. There was no evidence of amelioration of diuretic-induced hyperglycaemia.

Total Body Sodium

In an uncontrolled study, we demonstrated renal sodium retention during the first week of ACE inhibition. This was accompanied by water retention and weight gain. This early sodium retention was confirmed by double- blind studies when fluid retention and weight gain were also noted in the first 1-2 weeks after initiating ACE inhibitor. This early

sodium retention probably represents compensatory reflexes which attempt to preserve the mean arterial pressure during ACE inhibition. We noted evidence for increased proximal tubular reabsorption of sodium. An increase in anti-diuretic hormone and decline in atrial natriuretic peptide probably contribute to water and sodium retention.

In a controlled study, total body sodium was measured 6 weeks after the introduction of captopril. In this study there was no evidence that sodium balance had been altered in either direction. In a second study using enalapril, total body sodium decreased by about 100 mmol but this did not achieve statistical significance, nor was weight reduced.

It was notable in the enalapril study that symptoms such as postural hypotension were more common than in the study with captopril, and this may have reflected differences in sodium balance between the two studies.

Thus, ACE inhibitors initially cause sodium and water retention as noted above, which is limited by the improvement in cardiac function and the decline in plasma aldosterone, and perhaps angiotensin II and sympathetic nervous activity. During longer term ACE inhibition, the sodium "set point" appears to be altered, those reflexes enhancing renal sodium reabsorption decline[813] and a natriuresis takes place, reversing the initial sodium

retention. One mechanism for this may be a relative increase in atrial natriuretic peptide relative to the atrial pressure that has been observed. Another possibility is that the composition of the vascular wall may change, altering the relationship between arterial pressure and baroreceptor tone. It seems likely that this change from sodium retention to sodium excretion takes place between 1-2 months after initiation of therapy. Longer term ACE inhibition may lead to a net natriuresis, though this remains to be documented. The occurrence of postural hypotension many months after the institution of ACE inhibitor therapy would support such an idea.

Symptomatic improvement of heart failure with ACE inhibitors may be observed soon after instituting therapy, while exercise performance is demonstrably improved within 6 weeks. Thus, a natriuresis cannot be held solely responsible for the clinical benefits of ACE inhibitors, though they may enhance the long-term benefit. However, the fact that sodium retention is limited and reversed by ACE inhibitors may allow the beneficial effects of vasodilation to be displayed.

Total Body Potassium

Although serum potassium did not rise in the first week after ACE inhibition, renal potassium retention was prominent. During longer term ACE inhibition, we saw a consistent rise in total body potassium. This was directly

related to the initial extent of potassium depletion and to the initial activity of the renin- angiotensin-aldosterone system. This rise in total body potassium could not be accounted for by the rise in extracellular potassium which would only account for a 10-20 mmol increase in total body potassium. Intracellular potassium deficits must have been corrected.

The potassium deficits do not appear to be artefactual. The apparent potassium depletion could be corrected by an ACE inhibitor, the greatest rise in potassium being in those already potassium deplete. The relationship between potassium depletion and the renin-angiotensin- aldosterone system and the fact that the increase in potassium during ACE inhibitor therapy was directly related to pre-treatment renin also support the presence of a true potassium deficit.

Perhaps more striking than the increase in total body potassium was the change in the ratio of sodium to potassium which initially had been distinctly abnormal in patients with cardiac failure. Chronic ACE inhibition resulted in a significant increase in potassium in relation to sodium.

The increase in intracellular potassium may be important for several reasons. Presumably correction of deficits in the intracellular environment could improve cell metabolism

generally. Studies using nuclear magnetic resonance spectroscopy have suggested that the muscles of patients with heart failure may have a resting acidosis which worsens rapidly, even during light exercise. Restoration of intracellular potassium deficits could reduce intracellular hydrogen ion concentration and may delay the onset of exercise- induced intracellular falls in Ph. During exercise, serum potassium increases, potassium being released from the exercising muscle.[814] In the post-exercise period, this resolves rapidly, partly due to the high levels of sympathetic activity induced by exercise. In the presence of potassium depletion and sustained sympathetic activity observed in patients with heart failure, dangerous hypokalaemia may develop.[815] Repletion of muscle potassium may act as a buffer to stimuli which cause an acute decline in serum potassium.[816] Potassium deficits could also be partly responsible for the high incidence of arrhythmias observed in patients with heart failure. The myocardium may be protected from potassium depletion.[817] However, even if this is true it may not render it immune from the effects of potassium depletion elsewhere in the body. The presence of hypokalaemia and normal intra- myocyte potassium concentrations may be more unstable than if intra- and extracellular concentrations were reduced in concert.

Total Body Nitrogen, Calcium and Phosphorus

Total body calcium, phosphorus and nitrogen did not change during these studies. However, in both the study with

captopril and enalapril, an upward trend in total body nitrogen was observed. Clinical improvement, followed by improved mobility, may have had a training effect resulting in an increased skeletal muscle mass.

Total Body Chlorine

Total body chlorine was unchanged during long-term ACE inhibitor therapy. In studies both with captopril and enalapril, there was a downward trend in extra-cellular fluid volume which did not reach statistical significance, the magnitude of this effect being about 0.5 litres.

Total Body Oxygen

Total body oxygen, an index of body water, was unaltered by ACE inhibitors. This is consistent with the lack of change in weight. However, the downward trend of total body sodium and extracellular fluid volume in association with an unchanged total body oxygen suggests that intracellular rehydration may have occurred.

SUMMARY

I have defined the effects of converting enzyme inhibitors on serum electrolytes. Though the effects on serum potassium are consistent, at least during long- term converting enzyme inhibition, the effects on serum sodium are highly variable. In addition to simply raising serum potassium, ACE inhibitors can prevent acute falls in potassium in response to diuretics and in the post-exercise

period. This could be a result not only of inhibition of the renin-angiotensin system but also of secondary effects on the sympathetic nervous system.

Angiotensin converting enzyme inhibitors also have important effects on total body elemental composition. Total body sodium did not change for up to 2 months after starting an ACE inhibitor, suggesting that a natriuresis had not contributed directly to the benefits observed. Intracellular potassium deficits are at least partially corrected, as is the ratio of total body sodium to potassium. These changes in cell metabolism could contribute to the improvement in well-being and exercise performance experienced by patients established on ACE inhibitors.

CHAPTER 25: RENAL FUNCTION IN HEART FAILURE: THE EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

THE RENAL HAEMODYNAMIC CONSEQUENCES OF CARDIAC FAILURE

As cardiac output falls, so too does renal blood flow[818-821] In early heart failure, this is evident only during exercise,[819,822] while at rest renal blood flow, glomerular filtration rate and filtration fraction are normal. With worsening cardiac function, renal haemodynamics become relatively fixed, with a decline in renal blood flow and glomerular filtration rate. The portion of the total cardiac output distributed to the kidney also declines. Characteristically, glomerular filtration declines less than the renal blood flow, hence filtration fraction rises. Renal blood flow may be further compromised by arrhythmias commonly seen in heart failure.[823]

In experimental heart failure in animals, there is also a redistribution of blood flow, with a relative reduction in cortical, compared to medullary, flow. This results in a diversion of blood to the juxta- medullary nephrons, whose loops of Henle and associated vasa recta delve deep into the medulla and are responsible for counter-current exchange. These mechanisms may be important in maintaining sodium-poor, urea-rich urine, characteristic of heart failure. Such data as exists suggests that redistribution of renal blood flow in favour of the medulla also exists in humans, though most studies on renal function have been

carried out on patients treated with diuretics.[824-827] In addition to the fall in cardiac output, other factors that may affect renal blood flow in heart failure include an increase in sympathetic nerve activity,[828,829] angiotensin II, and atrial natriuretic peptide. Increased sympathetic activity could lead to afferent arteriolar constriction and a fall in renal blood flow and glomerular filtration. An increase in angiotensin II will lead to both afferent and efferent arteriolar constriction, with the predominant effect on the latter. This will lead to a decline in renal blood flow but with a relative preservation of glomerular filtration and an increase in filtration fraction.

Atrial natriuretic peptide may increase glomerular filtration and renal blood flow, but, like several other actions of this peptide, its effects appear to be over-ridden by other factors.[830,831]

Angiotensin II may have other intra-renal effects, including contraction of the glomerular mesangium, alterations in the intra-renal distribution of blood flow, and contraction of the vasa recta, which are discussed in Chapter 2.

Finally, especially in the context of angiotensin-converting enzyme inhibition, that renal blood flow and glomerular filtration rate fall steeply as the blood pressure falls below the auto- regulatory threshold.

THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS ON RENAL FUNCTION IN HEART FAILURE

On reviewing the literature on the effects of angiotensin-converting enzyme inhibitors on renal haemodynamics, the picture is somewhat confusing. Perhaps this is because of the complex nature of the problem. The effects of angiotensin-converting enzyme inhibitors on renal function depend on the duration of therapy, on the renal perfusion pressure, and on the prior state of activation of the renin-angiotensin system. Furthermore, angiotensin-converting enzyme inhibitors do not only suppress the formation of angiotensin II but also have complex effects on other systems.

ACUTE STUDIES ON THE RENAL HAEMODYNAMIC EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

On reviewing the acute studies, Creager et al[832] noted an increase in renal blood flow 1-2 hours after captopril, no change in glomerular filtration rate, and an increase in urinary sodium excretion. Similarly, Faxon et al[833] reported an increase in renal blood flow, 30-90 minutes after 25-100 mg captopril, while glomerular filtration rate was unchanged. A "substantial" natriuresis was reported. Powers et al[834] reported an increase in renal blood flow 24-48 hours after starting captopril, with no change in glomerular filtration rate, weight or sodium excretion. In contrast,

Mujais et al[835] noted a fall in renal blood flow 1-2 hours after 25 mg captopril; renovascular resistance fell, but not sufficient to compensate for the fall in arterial pressure. Glomerular filtration rate fell markedly, as did filtration fraction and sodium excretion. After one week of therapy and during long- term therapy, these effects were reversed.

MEDIUM-TERM STUDIES ON THE EFFECTS OF ACE INHIBITORS ON RENAL FUNCTION IN HEART FAILURE

On reviewing the medium-term studies (less than 10 days), a somewhat different picture emerges. Pierpoint et al[836] noted sodium retention and hyponatraemia developing in the first 3 days after starting captopril; glomerular filtration rate was unaffected. Kubo et al[837] noted a rise in renal blood flow one week after initiating captopril that was most marked in patients with high baseline plasma renin. Infusion of aprotinin, a kallikrein inhibitor, to suppress any increase in bradykinin after administration of captopril, failed to diminish the increase in blood flow. Dzau and Hollenberg[838] found an increase in renal blood flow and glomerular filtration rate 5 days after starting captopril in a group of patients with hyponatraemia. One group of patients had diuretics withdrawn for a 5- day period and showed similar haemodynamic changes. In those patients treated with diuretics and captopril, body weight declined and serum sodium concentration increased, while

those who received captopril alone increased their body weight and serum sodium did not change. Packer et al[839] also observed a correction of hyponatraemia with captopril which began 48 hours after starting therapy. However, Nicholls[810] et al reported a fall in serum sodium concentration over the first week of therapy in conjunction with a fall in urinary sodium excretion, implying inappropriate water retention. Fitzpatrick also reported a fall in serum sodium concentration and renal sodium retention in the first few days of treatment with enalapril, while glomerular filtration rate was unchanged.[811]

Our studies support the view that renal blood flow increases, both in absolute amount and as a proportion of the total cardiac output in response to the introduction of an angiotensin-converting enzyme inhibitor. Glomerular filtration rate tends to decline in the first few days of treatment with an angiotensin- converting enzyme inhibitor, and this is attended by a fall in urinary sodium excretion and a reduction in free water clearance and serum sodium concentration. Some of these patients developed new peripheral oedema. Sodium and water retention were most marked during the initial decline in arterial pressure. As sodium and water retention progressed, arterial pressure increased and a new balance was achieved at an expanded blood volume over the following 1-2 weeks.

We also noted a significant increase in weight after one

week of therapy with enalapril in a double-blind study. One patient developed frank worsening of his oedema. This subsided without the need to change the dose of diuretics over a 2-week period. Other double-blind placebo-controlled studies have also noted weight increases, necessitating an increase in diuretics on introduction of an angiotensin-converting enzyme inhibitor.[840] It is surprising that this problem is not more widely recognised clinically. This perhaps reflects the fact that many patients start angiotensin- converting enzyme inhibitors at a time when diuretic doses are being adjusted for other reasons and that symptoms may improve after introduction of an angiotensin-converting enzyme inhibitor despite fluid retention as long as it is not of a limited extent.

In the short-term studies on enalapril, we examined the interaction of diuretics and angiotensin-converting enzyme inhibitors on renal function. This demonstrated a significant interaction of frusemide and enalapril on renal haemodynamics. It is not clear whether other investigators have controlled for this effect. Patients with marked falls in arterial pressure and patients with pre-renal uraemia may behave differently also. Thus, therapeutic interactions and differences in the population under study could account for the discrepancies in the studies on renal haemodynamics mentioned in this section.

CHRONIC EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON RENAL HAEMODYNAMICS IN HEART FAILURE

Glomerular Filtration Rate

Apart from our double-blind, placebo-controlled, crossover studies, there are only 2 other studies which have investigated the long-term effects of angiotensin-converting enzyme inhibitors on glomerular filtration rate in heart failure.[835,841] These open evaluations both showed a tendency for glomerular filtration rate to rise with sustained treatment. They make no comment as to the timing of their studies in relationship to diuretic dose. In contrast, in our controlled studies we showed a consistent decline in glomerular filtration rate, whether measured by isotopic methods, by 24-hour urinary creatinine clearance, or by the measurement of serum urea and creatinine.

The cause of the decline in glomerular filtration rate has several possible explanations. Firstly, a fall in renal perfusion pressure without a change in efferent arteriolar tone to maintain glomerular hydrostatic pressure could result in a fall in glomerular filtration rate. However, the fall in renovascular resistance and a rise in renal blood flow suggest this explanation is incomplete. It is more likely that a reduction in angiotensin II, with a loss of efferent arteriolar tone, would lead to a fall in renovascular resistance and glomerular hydrostatic pressure together, and this would result in a decline in glomerular

filtration rate. Angiotensin II also has complex effects on the mesangium, but as most of these would appear to depress, rather than increase, glomerular filtration rate, this also seems an unlikely mechanism for the reduction in glomerular filtration rate during ACE inhibition.

Renal Blood Flow

Our studies concur with other studies of the long-term effects of angiotensin-converting enzyme inhibitors on renal blood flow. Renal blood flow not only rises but the proportion of cardiac output distributed to the kidney appears to increase.

The rise in renal blood flow with the fall in glomerular filtration rate suggests that it was predominantly efferent arteriolar tone that was reduced. However, afferent arteriolar tone may have been reduced also which would account for the beneficial renal haemodynamic effects of angiotensin-converting enzyme inhibitors observed in some studies of patients with pre-renal uraemia.[841]

This is consistent also with the finding that the fall in renal vascular resistance after an angiotensin- converting enzyme inhibitor was inversely related both to the initial angiotensin II and the initial plasma noradrenaline concentrations.

Filtration Fraction

Filtration fraction is the ratio of glomerular filtration rate to effective renal plasma flow and it is normally increased in cardiac failure. Our studies suggest that the renal "hallmark" of angiotensin- converting enzyme inhibitors is a decline in filtration fraction. However, the filtration fraction is complexly related to renal perfusion pressure and afferent and efferent arteriolar tone. No good relationship was found between other variables and the decline in filtration fraction. The decline in filtration fraction may represent a haemodynamic spectrum, one end being represented by a marked decline in glomerular filtration rate, with relatively little change in renal blood flow, the other end of the spectrum being a maintenance of glomerular filtration rate, with a marked rise in renal blood flow. Both patterns were observed in our studies, leading to a decline in filtration fraction.

The decline in filtration fraction is likely to reduce the oncotic pressure of fluid passing into the proximal renal tubules and could reduce proximal tubular salt and water reabsorption.

INTERACTION OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND DIURETICS ON RENAL HAEMODYNAMICS IN HEART FAILURE

During the long-term study on enalapril, we noted consistent declines in isotopically measured glomerular filtration rate which were highly consistent with the decline in 24-hour creatinine clearance. Fortunately, at the outset of this study we had addressed the question of timing of diuretic administration and had decided that all patients should be established on a twice-daily diuretic dose. Thus, all patients had their renal function assessed radio-isotopically in the presence of both an angiotensin-converting enzyme inhibitor and diuretic. However, in the study on captopril some patients were on once-daily and some on twice-daily diuretic regimes, in conjunction with 3 times/day captopril. We noted that those patients who were on twice-daily diuretic regimes and therefore had their renal isotope studies performed during concomitant angiotensin-converting enzyme inhibitor and diuretic therapy had a much greater decline in glomerular filtration rate. Those patients who received an angiotensin-converting enzyme inhibitor without additional diuretic therapy had relatively little decline in glomerular filtration rate. We therefore undertook short-term studies on enalapril to investigate this further. This confirmed that the decline in glomerular filtration rate was much greater when an angiotensin-converting enzyme inhibitor and diuretic were

used concomitantly. The study also suggested that all the haemodynamic effects of an angiotensin- converting enzyme inhibitor were exaggerated by a diuretic. Thus, the decline in mean arterial pressure, total vascular resistance and filtration fraction were all greater on the combination, as was the rise in cardiac output, renal blood flow, and that proportion of the renal blood flow diverted to the kidney.

The decline in glomerular filtration rate may be attributed to a fall in angiotensin II-mediated efferent arteriolar tone and a further fall in renal perfusion pressure, resulting in a fall in glomerular hydrostatic pressure. Frusemide also appears to have vasodilator properties, perhaps mediated through the prostaglandin systems.[842-846] This study suggests that frusemide may reduce efferent arteriolar tone which is normally masked by a rise in angiotensin II.

In a study with enalapril, we studied renal haemodynamics at baseline, one week after the introduction of drug or placebo in a double-blind fashion and then 8 weeks after introduction, one week after a change-over to the alternative treatment, and again at 8 weeks after the change in treatment. We were thus able to examine the subacute and chronic effects of angiotensin-converting enzyme inhibitors on renal function and the effects of withdrawal of this treatment.

Plasma angiotensin II was equally suppressed during tests of renal function after one and 8 weeks of enalapril, despite the different doses of the drug. The glomerular filtration rate, mean arterial pressure and the filtration fraction were less depressed after one week's treatment than after 8 weeks' therapy. The rise in renal blood flow was similar at one and 8 weeks' treatment.

There are several explanations for these findings. Firstly, in our patients, weight increased in the first week after treatment. Fluid retention could have supported mean arterial pressure, either by expanding blood volume or by increasing vascular stiffness. This maintenance of mean arterial pressure could have preserved the glomerular filtration rate, and enhanced renal blood flow.

Many other possible explanations exist, including time-dependent effects on endothelial renin-angiotensin systems which we would not be able to detect. However, we know that angiotensin-converting enzyme inhibitors have powerful effects on sodium and potassium metabolism and a decline in vascular wall sodium might occur more slowly, eventually leading to a greater vasodilator capacity.

On withdrawing enalapril, which we did in a controlled fashion in 10 subjects, we noted that glomerular filtration rate returned to normal within one week but mean arterial pressure remained reduced and renal blood flow elevated,

despite plasma angiotensin II concentrations rising to pre-treatment levels.

It is possible that endothelial-converting enzyme is inhibited for longer periods than circulating levels but metabolic changes and changes in vessel wall composition are likely to occur over longer periods of time and may account for this apparent maintenance of some of enalapril's effects.

LONG-TERM EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION ON RENAL SODIUM HANDLING IN HEART FAILURE

No significant change in sodium balance occurred over a 6-8 week period. The technique available should have been able to detect changes of more than 100 mmol, even though a large amount of sodium is relatively locked in bone matrix. As body weight and mean serum sodium concentration were unchanged also, this supports the view that no diuresis had occurred over the study period.

INFLUENCE OF CONVERTING ENZYME INHIBITORS ON RENAL TUBULAR FUNCTION IN CARDIAC FAILURE

Proximal Tubular Function

In salt-replete normal humans during a water diuresis, there is evidence that angiotensin II in pressor doses increases proximal tubular sodium reabsorption. However, captopril had no effect on sodium excretion in these subjects.[847] Also Ichikawa et al suggested that proximal tubular fluid reabsorption is reduced during angiotensin-converting enzyme inhibition in rats with heart failure induced by left ventricular infarction.[848] However, these data cannot easily be extrapolated to human subjects with heart failure, who are usually on diuretics and in whom substantial falls in blood pressure can occur.

I have experimented with lithium clearance methods to estimate proximal tubular function in heart failure but my initial experience with this method suggested that it was unsatisfactory. Firstly, lithium can either suppress or enhance renin production.[849] Secondly, we found that frusemide substantially effected lithium clearance, an effect that has been previously noted in sodium-deplete normal volunteers.[850] Although we have not excluded the possibility that frusemide itself has an effect on proximal tubular function, this is not consistent with the present theories of frusemide's action on the renal tubule.

Phosphate clearance methods have been advocated as measures of proximal tubular re-absorptive[851] and we have demonstrated that in patients with heart failure frusemide has little effect on phosphate clearance. We examined the effects of one week of therapy with a converting enzyme inhibitor on phosphate clearance in patients with cardiac failure. The amount of phosphate found in the urine was expressed as a percentage of that filtered at the glomerulus, based on creatinine clearance, and this was used as an index of proximal tubular reabsorption. On introduction of an angiotensin-converting enzyme inhibitor to chronically diuresed patients, we noted, in conjunction with the reduction in urine volumes and sodium concentration, an increase in proximal tubular reabsorption. Thus, early sodium retention in response to a converting enzyme inhibitor appears to be due to increased proximal tubular sodium reabsorption, perhaps associated with an acute decline in glomerular filtration rate and therefore the amount of sodium filtered at the glomerulus. As blood pressure is restored, glomerular filtration rate and proximal tubular reabsorption will tend to return to baseline levels. The reasons for the increase in proximal tubular reabsorption are not clear. Very high levels of angiotensin II (probably higher than levels found even in severe heart failure) can cause a natriuresis, reduction of which could promote sodium reabsorption. Lower concentrations of angiotensin II appear to cause sodium retention and this reduction should enhance sodium

excretion.[847] A decline in filtration fraction and sympathetic activity would be expected to increase sodium excretion also. However, other mechanisms, such as the fall in arterial pressure and atrial natriuretic peptide, may overcome the above. Although a decline in plasma noradrenaline was observed reflecting overall sympathetic activity, it is possible that renal sympathetic activity increased in response to the fall in arterial pressure. An increase in renal sympathetic activity could have caused renal sodium retention. However, when prazosin and captopril are used in combination, renal sodium retention is not prevented. [857]

The mechanism of action by which atrial natriuretic peptide induces natriuresis is yet to be fully elucidated. It may inhibit the sodium-retaining effects of angiotensin II on the proximal tubule[852,853] and may directly reduce proximal tubular reabsorption[854], and certainly appears to have effects on the collecting duct.[855,856]

Distal Tubular Function

Aldosterone has powerful effects on sodium/potassium exchange in the distal tubule. The acute suppression of angiotensin II causes a marked fall in aldosterone. Suppression of aldosterone cannot have an over-riding effect on tubular sodium handling at the onset of angiotensin-converting enzyme inhibition. It may take

several days for the renal effects of an elevated aldosterone to wane. Though urinary potassium excretion declines abruptly after starting an angiotensin- converting enzyme inhibitor, so too does urinary sodium, therefore this may not be mediated by aldosterone. During long-term therapy with converting enzyme inhibitors, potassium rises due to the chronic suppression of aldosterone secretion. This in turn leads to some stimulation of aldosterone production which serves to limit the extent of potassium retention. Suppression of aldosterone probably limits the extent of sodium retention, and may have an important role in reversing initial fluid retention.

EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON RENAL DIGOXIN HANDLING

Serum digoxin rose during long-term treatment with captopril. Possibly due to the accompanying rise in serum potassium and the rather low initial serum levels of digoxin, no serious consequences were found in association with this problem.

In an open study on 12 patients, we specifically examined urea, digoxin and creatinine clearance before and one month after captopril in patients with treated heart failure. Although all 3 declined, urea and digoxin clearance declined more than creatinine clearance. Fractional

excretion of urea and digoxin filtered at the glomerulus therefore declined, indicating greater tubular reabsorption or reduced tubular secretion of these compounds during treatment with captopril in patients with heart failure.

EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS ON THE DISTRIBUTION OF INTRA-RENAL BLOOD FLOW IN PATIENTS WITH CARDIAC FAILURE

A gradient exists from outer cortex to inner cortex, with the filtration rate of the outer cortical nephrons being lower than that of the middle and deep cortical nephrons in both the rat and the dog. Redistribution of renal blood flow from the outer renal cortex to juxta- medullary nephrons may be a further important haemodynamic change occurring in heart failure leading to sodium retention. These functional changes are accompanied by a rise in renin content in the kidney which is relatively greater in the juxta-medullary nephrons. There is some evidence that captopril may reverse these haemodynamic abnormalities.

The deep cortical nephrons may be less responsive to changes in sodium balance. The superficial nephrons appear to have a greater ability to increase sodium excretion, whereas the deeper nephrons have a greater capability for sodium retention.

No information is available in human subjects with heart

failure but in humans with hypertension and in experiments on rats, captopril, like frusemide, appears to correct the maldistribution of renal blood flow, diverting more blood to the outer renal cortex.

Angiotensin II, either by its effects on the efferent arteriole or by direct effects, may slow blood flow through the vasa-recta which descend deep into the renal medulla. Initially, this slowing of blood flow through the vasa-recta will enhance counter-current exchange mechanisms, maintaining urea excretion despite the fall in glomerular clearance. More marked increases in angiotensin II will lead to afferent arteriolar constriction and a more profound reduction in medullary blood flow. Uraemia may then occur.

SUMMARY

The effects of angiotensin-converting enzyme inhibitors on renal function are complex. They cannot be viewed as entirely beneficial. In the early stages of heart failure, angiotensin II may be useful in maintaining glomerular filtration rate and urea excretion. Even in more profound heart failure the acute effects of angiotensin-converting enzyme inhibitors on renal function seem more deleterious than beneficial, sodium retention and an acute decline in glomerular filtration being prominent effects. However, in the longer term, despite a continuing slight reduction in

glomerular filtration, angiotensin-converting enzyme inhibitors do appear to enhance renal sodium excretion. The importance, if any, of the increase in renal blood flow and changes in intra-renal blood flow distribution have yet to be determined. The medium-to-long-term effects of angiotensin-converting enzyme inhibitors on the kidney appear to be fairly neutral. In the setting of vasodilatation, this "neutral" role of the kidney in sodium homeostasis after angiotensin-converting enzyme inhibition may be important.

CHAPTER 26: AUTONOMIC FUNCTION IN HEART FAILURE: THE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITION

Although the primary defect in the syndrome of heart failure is pump malfunction, the consequences of this defect leads to dysfunction in many other body systems. Indeed, it is probably essential for the evolution of heart failure that the vascular resistance is raised and that the blood flow to the kidney and skeletal muscle is depressed. This increase in vascular resistance is mediated not only by hormones such as angiotensin II, but also by the autonomic nervous system. However, neither can be considered in isolation. The sympathetic nervous system may not only stimulate the release of renin but angiotensin II may have vagolytic effects and modulate sympathetic activity. Angiotensin II and the sympathetic nervous system may have powerful interactive roles, especially on the venous systems. [254,259]

AUTONOMIC DYSFUNCTION IN HEART FAILURE

The pattern of autonomic dysfunction in heart failure is well characterised. Parasympathetic tone is reduced in patients with heart failure, while sympathetic activity, under resting conditions, is increased.[858-863] This autonomic imbalance may account for some of the characteristic features of heart failure such as tachycardia and arrhythmias, in addition to the increase in vascular tone.

Although basal sympathetic activity is increased in heart failure, sympathetic reflexes are characteristically blunted. For example, although resting heart rate is increased, heart rate does not increase on standing.[864]

The stimulus to increased sympathetic activity in heart failure is derived probably from high pressure baroreceptors that sense a relative reduction in arterial pressure or, at least, arterial wall tension.[865] Very high levels of sympathetic activity may be observed in pulmonary oedema but may be related more to stress and anxiety than to ventricular filling pressure.[866] However, stimulation of atrial stretch receptors can depress renal efferent sympathetic nerve activity.[73,78] In heart failure, reduced atrial compliance and morphological changes in the receptors themselves lead to reduced sensitivity.[867-869] Thus, a reduction in tonic inhibition of sympathetic nerve activity may be lost in heart failure. Finally, angiotensin II may have a facilitatory role on sympathetic nerve activity.[254,259] The reasons for the defect in sympathetic reflex responsiveness in heart failure are complex. The number of cardiac neurones may be reduced in patients with idiopathic cardiomyopathy and with Chaga's disease.[870] These abnormalities are probably fixed and unlikely to be restored by any therapeutic manoeuvre. Sympathetic nerve terminals within the heart are also abnormal, with evidence for defects in noradrenaline synthesis and turnover.[426,427]

Finally, down-regulation or uncoupling of adreno-receptors may reduce end-organ responses.[430-432]

The increase in sympathetic activity may have other important effects on the cardiovascular system. Excessive sympathetic tone may cause further myocardial damage. Some authors advocate the use of beta-receptor blocking agents for the management of ischaemic and non- ischaemic cardiomyopathy, suggesting direct beneficial myocardial effects. Beta-blockers could also reduce plasma renin.[80] Less is known of the origin of parasympathetic dysfunction in heart failure. Angiotensin II has vagolytic effects,[294-298] while digoxin is a parasympathomimetic[871-876] Resting parasympathetic tone appears to be low, while the increase in heart rate in response to atropine is reduced, as is the bradycardia in response to an increase in blood pressure. [860] This apparent loss of parasympathetic reflux response could be due to an actual or functional loss of cardiac innervation or autonomic defect in end-organ response. However, animal models of heart failure suggest that the sinoatrial node reacts normally to direct stimulation of the vagus nerves, suggesting that the efferent limb of the reflex is not impaired. [877] This suggests there must be a mechanism which interferes with the afferent and/or central modulation of parasympathetic activity.

TESTS REFLECTING PARASYMPATHETIC ACTIVITY

Normally, the heart rate varies continuously. This depends upon an intact parasympathetic nerve supply and therefore this beat-to-beat variation can be abolished by atropine but is uninfluenced by propranolol. (See Methods) Heart rate variability on ambulatory monitoring is reduced in patients with heart failure.[878] Deep breathing at 6 breaths/minute is a convenient and reproducible technique, deep inspiration resulting in an increase in heart rate. The heart rate variation is exaggerated by deep breathing, presumably due to more pronounced variations in venous return and inactivation of cardiopulmonary reflexes in response to larger changes in intra-thoracic pressure. In heart failure, where venous and intra-cardiac pressures are elevated, this effect is diminished. Consequently, autonomic reduction of the **STIMULUS** to variations in parasympathetic tone, rather than autonomic defect in detection or transduction of the signal, could explain this abnormality in heart failure.

During the strain period of the Valsalva manoeuvre, the blood pressure drops and the heart rate rises as venous return to the heart is impeded. Peripheral arterial constriction occurs in response to the fall in blood pressure. After release, the blood pressure rises, overshooting its resting value as cardiac output increases against the raised peripheral resistance; the heart slows. Again, the heart rate responses can be blocked by atropine,

but not by propranolol. (See Methods) In heart failure, cardiac output and blood pressure are maintained during the Valsalva manoeuvre as venous return does not decline. No overshoot of blood pressure nor fall in heart rate occurs on release of strain. This failure of parasympathetically mediated slowing of the heart rate could be due primarily to autonomic nervous system reflex dysfunction, but the lack of blood pressure overshoot means there is no primary parasympathetic stimulus in heart failure anyway.

During the change from lying to standing, a rapid increase in heart rate occurs, which is maximal about the 15th beat after standing, a relative overshoot bradycardia then occurs, maximal about the 30th beat. This response is also mediated by the vagus nerve. This test is dependent upon changes in venous return, a relative maintenance of which during the upright posture may account for the abnormality in heart failure.

Using the tests employed, it is difficult to say whether the defects in parasympathetic reflexes are due to an intrinsic defect in the reflex arc or are due to a reduction in the afferent stimuli due to changes in venous haemodynamics. However, other studies have demonstrated a reduced heart rate response to atropine in subjects with heart failure due to idiopathic dilated cardiomyopathy. As resting parasympathetic tone is reduce in heart failure, one might expect that the change in heart rate after

atropine should be reduced, but not the absolute level achieved. This suggests that other factors such as defective sinus node function, reduced sensitivity to the prevailing sympathetic tone, or the pharmacological effects of digoxin, may play a role. Indeed, all our subjects were on digoxin.

Reduced parasympathetic control of heart rate may be important. Several investigators have suggested that loss of heart rate variability, a sign of reduced parasympathetic activity, may herald serious ventricular arrhythmias.[879] Also, diabetic patients with autonomic dysfunction appear to have a higher risk of sudden death.[880]

TESTS REFLECTING SYMPATHETIC NERVOUS DYSFUNCTION: COMPARISON OF NORMAL SUBJECTS WITH PATIENTS WITH HEART FAILURE

Basal sympathetic nervous activity in heart failure is probably increased, as noted above. Sympathetic nervous activity may be further excited by the rise in angiotensin II, and by further contractions in plasma volume as a result of diuretic therapy.

We observed a significant increase in plasma noradrenaline after the administration of diuretic in patients with heart failure, and although we have no direct comparative information, other studies have shown this to be true in patients with hypertension given intravenous frusemide.[881]

On standing, venous pooling of blood causes a fall in blood pressure, which is normally rapidly corrected by venous and arterial constriction. The heart rate is also increased after 2 minutes of standing. These responses are largely dependent upon an intact sympathetic nervous system and are accompanied by an increase in plasma noradrenaline. Our results confirm these findings. In heart failure, the rise in heart rate and plasma noradrenaline on standing are blunted. This is probably due to a lack of venous compliance which prevents peripheral pooling of blood. Thus, cardiac output does not appear to fall on standing in patients with heart failure, while some have reported an increase in cardiac output associated with a fall in systemic vascular resistance. [882,883]

Although studies of autonomic reflexes in cardiac failure are of some interest, as the heart, the target organ for the disease under study, is the major determinant of the reflex, the results must be interpreted with a great deal of caution. Again, it is difficult to distinguish to what extent abnormal reflexes are due to cardiac malfunction and what are due to intrinsic alterations in sympathetic activity.

EFFECTS OF ENALAPRIL THERAPY

Tests of autonomic function in normal subjects, salt-replete and -deplete, have failed to reveal an effect of ACE inhibitors on sympathetic reflexes,[884,885] but do suggest an effect on parasympathetic autonomic reflexes. In contrast, one study in subjects with heart failure suggested the reverse.[589] However, this study was not placebo-controlled and improvements in the response to the Valsalva manoeuvre did occur, although the author dismissed them.

During long-term therapy with enalapril, basal supine heart rate was reduced, most probably due to a reduction in sympathetic drive, as suggested by the decline in plasma noradrenaline, although an increase in parasympathetic tone may also have occurred. The increase in supine heart rate and plasma noradrenaline that occurred later in the day, after diuretics, was also inhibited by enalapril.

However, on standing, systolic blood pressure fell more on enalapril compared to placebo, and this was accompanied by a significantly greater increase in heart rate and plasma noradrenaline on assumption of the upright posture. The changes in heart rate and plasma noradrenaline on standing during long-term enalapril therapy were similar to those in normal controls. Though this may suggest a return of autonomic function to normal, it could also indicate that a greater stimulus to sympathetic afferents occurred after

enalapril therapy. Sequestration of blood in the peripheral veins and consequently a greater fall in blood pressure could have contributed to the "improvement" in this sympathetic reflex after treatment with enalapril. Additionally, a greater fall in atrial pressure could activate renal sympathetic efferents.

The heart rate and blood pressure response to isometric exercise and cold pressor testing were unchanged by enalapril.

Systolic blood pressure was reduced at all levels of exercise during enalapril therapy. Heart rate, measured at the same stage of exercise, was lower during enalapril therapy, though the peak exercise heart rate was slightly faster. Plasma noradrenaline measured at the end of exercise was not changed by enalapril therapy. It is difficult to interpret these observations as patients exercised significantly longer on enalapril. A reduction in heart rate or sympathetic activity measured at the same stage of exercise could therefore be appropriate to the percentage of maximal exercise capacity rather than be due to a reduced sympathetic responsiveness. Thus, we were not able to confirm reduced sympathetic activation during exercise as has been suggested by others.[886] Other investigators have studied cardiac sympathetic activity by measuring coronary sinus catecholamine levels and the transmyocardial (coronary) changes both at rest and during

exercise.[887] These studies are in agreement that, at rest and during exercise, long-term treatment with an ACE inhibitor reduces cardiac sympathetic activity. However, it is possible that ACE inhibitors increase renal sympathetic activity during exercise and that renal excretion of catecholamines is also reduced.

However, although we were not able to demonstrate any differences in plasma noradrenaline immediately after exercise, plasma noradrenaline did seem to fall more rapidly after exercise in patients treated with enalapril. This parallels the changes found in normal subjects and is contrasted with the sustained high levels of plasma noradrenaline seen in patients with heart failure not receiving an ACE inhibitor.

Therefore, although resting sympathetic activity appeared to be reduced during treatment with enalapril, the improvements noted in some sympathetic reflexes must be interpreted with caution.

Tests of parasympathetic function were generally improved by long-term therapy with enalapril in patients with heart failure. A sudden increase in parasympathetic tone due to a loss of the vagolytic action of angiotensin II may also be responsible for the sudden fall in heart rate seen during hypotension after the first dose of an ACE inhibitor. There are several possible explanations for

these effects on sympathetic and parasympathetic function:

1) Angiotensin II might itself cause the derangement in parasympathetic and sympathetic functions seen in heart failure. Angiotensin II is known to inhibit parasympathetic activity and also facilitate cardiac sympathetic noradrenaline release. Chronically elevated sympathetic activity may cause adrenergic receptor down-regulation or uncoupling. Angiotensin II could then give rise to the picture of elevated basal sympathetic activity, but reduced sympathetic responsiveness.

Angiotensin-converting enzyme inhibitors, by suppressing angiotensin II, could also increase parasympathetic tone. There is considerable evidence that this is the case in animal experimental models.

A decrease in angiotensin II might lead to a fall in basal sympathetic activity and thus to up-regulation of adrenergic receptor sensitivity. A reduction in angiotensin II might conserve cardiac stores of noradrenaline also. Thus, a reduction in angiotensin II could lead to reduced basal activity but an increased response to physiological stress. This is probably highly desirable.

2) An improvement in autonomic function may have been a non-specific response to the improvement in heart failure. For instance, an increase in cardiac vagal afferent

activity mediated by ventricular baroreceptors may result from a reduction in diastolic filling pressures.[72,73] Changes in contractile force and ventricular compliance may also affect autonomic function.

3) The improvement in the tests might reflect effects upon the arterial system. Changes in arterial wall tension rather than the pressure itself may be the primary stimulus to baroreflexes as arterial wall tension is directly proportional to the pressure and the radius of the artery. Therefore, if blood pressure falls and the artery dilates, transmural wall tension may be unchanged; a dilated, more compliant, arterial system may then reduce the stimulus of a fall in blood pressure to the baroreceptors. We have only examined autonomic reflexes during chronic angiotensin converting enzyme inhibition. Changes in vascular wall composition may occur during long-term treatment which could have profound implications for activation of the sympathetic nervous system and ultimately renal sodium handling.

4) Increased venous compliance could have increased the stimulus to the afferent limb in those tests in which peripheral pooling of blood provides the stimulus to the cardio-pulmonary receptors. The effects of upright posture, Valsalva manoeuvre, and deep breathing in particular could be affected by this mechanism.

5) There may be changes in the baroreceptor or efferent organs themselves.

6) Digoxin is known to stimulate parasympathetic activity, which may have been unmasked by suppression of angiotensin II. Digoxin may have other effects on patients with heart failure, including a reduction in plasma renin, direct vasoconstriction, direct sensitisation of baroreceptors, and indirect sensitisation of ventricular baroreceptors by digoxin's positive inotropic effects.[873] However, as digoxin therapy was unchanged throughout this study and the increase in serum digoxin small during enalapril therapy, it is unlikely that any of the above could be relevant to the changes observed during chronic enalapril therapy.

EFFECTS OF ENALAPRIL ON QTC

The baseline QT interval was prolonged in those patients with heart failure; approximately 80 milliseconds greater than in the control group. The underlying myocardial disease, alterations in the balance of cardiac sympathetic tone, and reduced serum potassium could have accounted for this. The one patient who was on amiodarone was excluded from this part of the study but did have a markedly prolonged QT interval. A large component of the QT prolongation was due to an increase in the QRS width, though only one patient had complete left bundle branch block. This was corrected for by subtracting the QRS width

from the QT interval to give the JT interval. The JT interval was found also to be greater than the mean value for normal subjects. Though enalapril did not alter the uncorrected QT interval significantly, heart rate fell during treatment with enalapril, leading to a reduction in QTc. This was due to a reduction in the JTc interval rather than an alteration in QRS width. This shortening of QTc may have been due to the reduction in cardiac volumes, changes in autonomic tone, and the rise in serum potassium. The implications of this will be discussed further on in the section on arrhythmias.

SUMMARY

In summary, changes in most sympathetic and parasympathetic reflexes are observed during chronic converting enzyme inhibition. In general, these reflexes are improved, resembling more closely responses seen in normal subjects. However, it is difficult to be certain that these changes represent a restoration of normal physiology. Many, if not all, of the improvements could represent a pharmacological response to vasodilator therapy.

CHAPTER 27: SYMPTOMS

Over the last 5 years angiotensin-converting enzyme inhibitors have evolved from a promising therapeutic intervention into an established treatment for heart failure. The series of experiments in this thesis reflects the progress in our understanding of heart failure, the renin-angiotensin system, and of the use of converting enzyme inhibitors over this period. While many questions regarding the use of angiotensin- converting enzyme inhibitors in heart failure have been answered, I believe we have still only a crude understanding of their mechanisms of action and their optimal use.

SYMPTOMS IN HEART FAILURE

The mechanism(s) of the induction of symptoms in heart failure is/are incompletely understood. Exercise performance relates poorly to resting, peak exercise, or the change in atrial pressures in patients with heart failure.[888,889] The same is true of left ventricular ejection fraction, while initial reports of a relationship between right ventricular ejection fraction and exercise duration have not been confirmed.[890-892] Exercise cardiac output does correlate fairly well with exercise duration[889,889] but a causal relationship has not been demonstrated. The peak achieved cardiac output could reflect the output required for that level of exercise, the patient stopping for reasons unrelated to cardiac output itself. It is clear

that many patients with heart failure stop exercising before respiratory indices such as the "anaerobic" threshold and the "VO_2 Max" have been reached, suggesting that maximum cardiac performance has not been achieved. Certainly, breathlessness in chronic cardiac failure seems poorly related to most measurements of cardiac haemodynamics, either at rest or during exercise.

However, the possibility of a disorder of cardio- pulmonary haemodynamics being the root cause of breathlessness should not be rejected too easily. The duration of heart failure and the relative change of haemodynamic variables from rest to exercise must play some role in the induction of symptoms. For instance, the patient with previously normal left ventricular function developing a large myocardial infarction, with a rise in left ventricular filling pressures, might very well develop pulmonary oedema, with a left atrial pressure of 20-25 mm Hg. Patients with heart failure often tolerate left atrial pressures of 30-40 mm Hg without evidence of pulmonary oedema. Changes in pulmonary capillary permeability, the quality of the interstitial pulmonary tissues, and changes in pulmonary lymphatic drainage, may all operate to the patient's advantage in heart failure, at least at rest. Patients may develop these protective mechanisms to differing degrees. This is exceedingly difficult to take into account in haemodynamic studies.

During exercise, a rise in circulating lactate occurs at much lower workloads than in normal subjects.[893,894] This tendency to produce a metabolic acidosis may lead to an increase in ventilation which in turn will reduce arterial carbon dioxide tensions (pCO_2) and return hydrogen ion concentration towards normal.[895] A change in the relationship between exercise workload and ventilation could then lead to the sensation of breathlessness. This must only be part of the story as at maximal exertion ventilation and blood lactate levels are far higher in normal subjects than in patients with heart failure.[896] Moreover, some authors have failed to find a fall in arterial pCO_2 despite a relative increase in ventilation in patients with heart failure, which suggests that there may be an increase in the physiological dead-space due to ventilation/perfusion mis-match in such patients.[896]

A pulmonary rather than a cardiac abnormality could be the underlying cause of symptoms in heart failure. Firstly, despite an increase in ventilation which should raise end-tidal and alveolar oxygen tensions, arterial oxygen tension pO_2 remains constant in patients with heart failure.[890,897] This implies a widening of the alveolar-arterial oxygen gradient, and the possibility of a pulmonary diffusion block. Opinions are divided as to whether a fall in arterial pCO_2 occurs.[890,898] If one accepts that pCO_2 falls during exercise in heart failure then this implies that a diffusion block to oxygen or

ventilation-perfusion mis-match exists. If one accepts the evidence that pCO_2 is unaltered, then a diffusion block is likely. Any obstruction to diffusion would have to be moderately severe as the transit rate of blood through the pulmonary capillaries is likely to be reduced in heart failure. Extravasation of fluid due to a change in capillary pressure, a change in capillary permeability, reduced lymphatic clearance and possibly chronic changes which lead to thickening of the tissue barrier between the alveoli and the capillary blood will reduce the diffusing capacity for oxygen. Another potential pulmonary mechanism related to breathlessness and exertion in heart failure is an increase in airways resistance.[899,900] Bronchial hyper-responsiveness to the inhalation of methacholine, a muscarinic receptor agonist, in patients with heart failure has been documented. The reasons for this response are unclear but an increase in bronchial mucosal blood flow caused by methacholine may increase the thickness of the bronchial wall and reduce bronchial calibre. Alternatively, a chronic reduction in vagal activity could lead to receptor super-sensitivity. The effects of methacholine can be reversed by inhalation of methoxamine but not by optimising diuretic therapy.[900] Interestingly, hypocapnia is a broncho-constricting stimulus which is thought to be mediated through muscarinic receptors.[901] Alterations in lung "stiffness" could also contribute to symptoms of breathlessness by activating juxta-pulmonary capillary receptors.[902] However, decreased lung compliance does not

correlate with the degree of breathlessness.[903,904]

Of course, many patients are limited by symptoms other than breathlessness during exercise, predominant among these is fatigue. Though skeletal muscle blood flow is impaired at rest in more severe cases of heart failure, it is reduced during exercise.[905,906] Femoral vein oxygen saturations are reduced to very low levels, and this seems to correlate with fatigue. This suggests that an inadequate blood supply to exercising muscle may be the origin of fatigue and the limiting factor for exercise. A reduced oxygen supply will lead to tissue hypoxia, acidosis, local lactate accumulation, and a depletion of high-energy phosphates.[907,908,910] As skeletal muscle blood flow is dependent on the cardiac output, this may be the reason why cardiac output, minute oxygen consumption, and exercise performance, are related. Relative regional vascular resistance must also govern what proportion of the cardiac output supplies skeletal muscle. However, some relative increase in limb vascular tone is probably necessary in heart failure to prevent exertional hypotension, with a consequent fall in cerebral perfusion and syncope. A reduction in limb vascular tone may also be undesirable if it is not diverted to exercising muscle. This appears to be a problem with some vasodilator agents.[911]

Another probable contributory factor to the symptoms of heart failure is that most patients are not only unhealthy

but also unfit. Training programmes can improve patients' exercise performance and improve symptoms of fatigue and breathlessness.[912,913] Interestingly, peak exercise cardiac output increases after a period of training, again suggesting that it is not cardiac output per se that is limiting exercise in heart failure. Changes in skeletal muscle metabolism and perhaps vascular tone induced by the relative immobility of the patient may make a major contribution to exercise performance.

Finally, the problem which probably confounds success in discovering the origin of symptoms in heart failure more than any other is the relationship between the type of exertion and symptoms. Exercise that requires bursts of exertion at high workload are commonly terminated by breathlessness, while those that involved prolonged low-level exertion are terminated by fatigue.[914] Measurement of gas exchange during a short period of high-level stress demonstrates that the patient makes a maximal cardio-respiratory effort. In contrast, during protocols which involve much slower increases in speed and incline, many patients do not achieve maximal cardio-respiratory stress or cross the so-called anaerobic threshold. Of course, what is low-level exercise for some patients with heart failure represents a maximum effort for others. Most studies suffer from studying patients using only one exercise protocol. Inevitably, the same protocol requires different forms of exertion for different patients.

Thus, from studies on respiratory gas exchange, there does appear to be a closer relationship between breathlessness and maximal cardiac stress when compared with the symptom of fatigue. Though there is little information in this area, it is likely that changes in fatigue are most closely associated with changes in the peripheral circulation and skeletal muscle metabolism. In particular, changes in skeletal muscle potassium and energy stores in the form of ATP and ADP.[908,909]

THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN PATIENTS WITH HEART FAILURE

We have confined ourselves to the study of more severely symptomatic patients with heart failure. Studies in milder degrees of heart failure have also been encouraging,[915] though the use of converting enzyme inhibitors without diuretics in heart failure remains highly controversial.[916,917] In our studies, breathlessness was the symptom most consistently improved.

As demonstrated by ourselves in an acute study, and by others in long-term studies,[918] converting enzyme inhibitors favourably affect cardiac haemodynamics in heart failure, increasing cardiac output and reducing left ventricular filling pressure. However, symptoms may not improve for

several months after instituting an ACE inhibitor, and certainly appear to continue to improve with time.[919,920] In contrast, there is relatively little difference between the acute and chronic haemodynamic effects of ACE inhibitors in the majority of patients.[918] Therefore, central haemodynamic changes alone fail to explain the reduction in breathlessness with ACE inhibitors.

A potential beneficial effect of ACE inhibitors upon ventilation/perfusion mis-match or bronchial hyper-reactivity has not yet been observed, though neither has it been specifically investigated as far as I am aware. Angiotensin-converting enzyme inhibitors can have pulmonary effects such as cough. Using the capsacein test this can be observed in up to 15% of cases.[921] However, no relationship between cough sensitivity and beneficial effect has been noted.

The effects of angiotensin-converting enzyme inhibitors on skeletal muscle blood flow during exercise are subject to controversy.[922-925] Some have observed no effect, others an improvement. Some suggest that an increase in skeletal muscle blood flow is only observed in those who improve and that the relationship is causal. However, this line of argument is not tenable. Skeletal muscle blood flow could have been higher because the patient exercised for longer.

It is likely that "training" effects are important in the genesis of the beneficial effects of ACE inhibitors. The restriction in activity enforced by the patient's breathlessness must have a "detraining" effect, as with any sedentary life-style. This is reflected in evidence of impaired muscle strength and impaired muscle metabolism in cardiac failure.[926] Improvements in peripheral muscle metabolism have been noted after starting patients with heart failure on captopril. However, the mechanism which allows the patient to "retrain" while receiving an ACE inhibitor is unknown. Perhaps minor improvements induced by central or peripheral haemodynamic effects allow the patient to tolerate more exercise, setting up a beneficial spiral. Another possible mechanism of improvement in patients with heart failure is the induction of a natriuresis by the ACE inhibitor. Cowley et al have shown that increasing the diuretic is as effective in improving symptoms and exercise performance as adding an ACE inhibitor.[927] The effects of studying long-term sodium metabolism are, of course, exceedingly difficult. However, using in-vivo activation analysis, we were unable to demonstrate any negative sodium balance in the first 6-8 weeks after starting an ACE inhibitor, although a beneficial effect on the sodium/potassium ratio was observed. In contrast, in the first week after starting a converting enzyme inhibitor, if diuretics were left unchanged, sodium balance is positive. Milder degrees of sodium retention during addition of an ACE inhibitor appear

compatible with simultaneous clinical improvement. However, more severe degrees of sodium retention may lead to clinical deterioration in the patient's heart failure, with increasing ankle swelling, breathless, and fatigue.

Finally, a psychological effect of ACE inhibitors leading to an increase in physical activity and a secondary training effect has not been excluded.[928] This would be difficult to do in patients with heart failure. An improvement in symptoms is at least as likely to improve psychological well-being as the converse. Studies in hypertension have shown improvements in psychological status during treatment with ACE inhibitors.[929] Much, if not all, of this effect may be due to withdrawal of other therapies such as beta-blockers. However, it is possible that diuretics have subtle effects on the psyche and that these may be ameliorated by ACE inhibitors.

Ankle swelling was not a prominent feature in the patients in our studies. In patients who were already severely symptomatic, it was felt unethical not to try and optimise their diuretic dose. It was unlikely that we would observe any improvement in ankle swelling in these studies, and, indeed, this proved to be the case, though a certain number of patients did show temporary increases in ankle swelling.

Not all studies have confirmed an improvement in symptoms

in patients with heart failure treated with converting enzyme inhibitors.[930,931] Of course, some differences are to be expected due to random sampling, but, of note, our study in patients who had heart failure and angina and one further study which specifically studied patients with ischaemic heart disease, failed to show symptomatic benefit. In our study, we demonstrated deterioration in the symptom of angina. This was associated with a failure of exercise performance to improve. Breathlessness and fatigue were also unchanged. It is probable that resting haemodynamics were improved in these patients but exercise haemodynamics may well have been unchanged due to the further impairment of left ventricular function due to myocardial ischaemia. One of the implications from the study on angina is that changes in exercise haemodynamics and metabolism may be more important than those at rest.

In summary, the origin of symptoms in heart failure and the reason for the beneficial effects of ACE inhibitors on exercise are probably multi-factorial. Major methodological problems in the assessment of symptoms have retarded progress to date.

CHAPTER 28: EXERCISE PERFORMANCE

In two separate double-blind placebo-controlled studies, I have demonstrated that ACE inhibitors improve the exercise performance of patients with congestive heart failure. This concurs with other studies which incorporated larger number of subjects but used a single-leg design.[932] Using a cross-over design, as in our studies, not only are the number of comparisons per patient doubled but, as the patient is compared with him/herself, inter-individual variability is reduced. Thus, it is likely that a cross-over study design has several times the power of a single-leg study to demonstrate differences in patients with heart failure. The syndrome called heart failure varies markedly from patient to patient in terms of the pattern and inter- relationships of symptoms, signs, and central and peripheral haemodynamics. Therefore, a cross-over study design may considerably enhance the ability to detect clinically important differences in this heterogenous population. A further problem with large scale studies designed to test for improvement in symptoms and exercise performance is that irrelevant differences may be discovered. Small improvements requiring a large study population to detect change are unlikely to impress either the patient or clinician. Likewise, a treatment that benefits symptoms in only one patient in ten is unlikely to have a major impact on the management of heart failure. Controlled trials are necessary in heart failure as the

placebo response may be very marked, and this is an argument in favour of cross-over study designs, but the need for very large studies to demonstrate a change in symptoms or exercise performance is ethically and economically questionable. Large studies are valuable in determining an effect on progression of disease and mortality. Double-blind cross-over studies do have problems. They may produce carry-over effects from one treatment phase to the other, or the patient's underlying condition may improve or deteriorate. However, "order" and "period" effects were not noted in our studies. The impact of patients dropping out of the study in a cross-over study design will be much greater as each individual represents a higher proportion of the overall study and much more data are "lost". In order to reduce the likelihood of "drop-outs", treatment phases have to be relatively short, though we had a very low drop-out rate with treatment periods of up to 2 months, with a total study duration of 4 months. As with any study design, there are flaws, but the use of cross-over studies is best as long as very long-term effects are not being studied.

Single-blind studies have also examined the time-course of the effect of ACE inhibitors on exercise performance. Serial exercise testing has shown a progressive improvement in exercise performance, significant differences appearing at about 5 weeks and increasing up to at least 3 months.[933] Our studies demonstrating improved exercise performance at

6-8 weeks are entirely compatible with this. However, it was impossible to distinguish whether improved exercise tolerance was due to a reduction in fatigue or breathlessness, though symptom scores for the patients day-to-day experience suggested that breathlessness was more improved than fatigue. The application of multiple exercise protocols could have been helpful in determining if ACE inhibitors had a greater impact on one particular limiting symptom during exercise testing.

As discussed in the section on symptoms, what limits exercise in patients with heart failure is still largely unknown. Therefore, the mechanism by which ACE inhibitors improve exercise has not been determined.

It does appear that an additional natriuresis was not the cause of improved exercise performance as there was no change in total body sodium status at 6-8 weeks' treatment with an ACE inhibitor, when exercise performance had clearly improved. This was further confirmed by a lack of change in the patients' weight.

In the introduction to this thesis, I argued that evidence that vasodilator agents improved patients with chronic heart failure was lacking. Accordingly, it cannot be assumed that ACE inhibitors have brought about benefit due to vasodilatation. However, arteriolar dilators reduce arterial and renal perfusion pressure which may cause

sodium retention, possibly, though not necessarily, by activating the renin-angiotensin system. Likewise, venodilatation may reduce atrial pressures and reduce atrial natriuretic peptide, leading to sodium retention. Indeed, we have demonstrated this with ACE inhibitors. Angiotensin converting enzyme inhibitors cause arteriolar and venous dilatation, and early in the course of therapy may also reduce sodium excretion. However, by interrupting the production of angiotensin II, with all its consequences, ACE inhibitors limit the intensity of sodium retention and eventually reverse it, restoring the status quo. Angiotensin converting enzyme inhibitors may even cause a net diuresis if given for long periods of time. It is not entirely clear if this is merely an effect of aldosterone suppression or a more subtle resetting of the sodium "set-point". The combination of vasodilatation and inhibition of secondary sodium retention may be what makes ACE inhibitors uniquely effective among vasodilator agents.

Structural changes in the arterial wall which occur in heart failure could also be reversed by ACE inhibitors,[934,935] improving exercise blood flow, while ACE inhibitors prevent the rise in angiotensin II seen during exercise and may moderate the increase in sympathetic activity. However, the effects of ACE inhibitors on skeletal muscle blood flow during exercise are controversial. Certainly, increases in limb blood flow are not impressive generally.[936-939] Some

authors have suggested that it is only those patients in whom exercise limb blood increases that demonstrate an increase in exercise performance. However, again the problem arises, does an increase in exercise performance induce a high limb blood flow or the inverse? Angiotensin converting enzyme inhibitors could have improved exercise performance by a "training" effect, though the mechanism which initiates it is unclear. An improvement in general well-being could be a factor. Improvement in central haemodynamics may be enough to allow slightly more exercise, too small to detect with our techniques, but which leads to a positive feedback.

Changes in skeletal muscle metabolism are well described in heart failure, which are probably in a large part due to "disuse".[940] An additional effect may be due to under-perfusion, leading to an early intracellular acidosis and loss of high energy phosphates.[941] Finally, we have suggested that a true intracellular deficit of potassium exists in heart failure, which could impair skeletal muscle performance. Angiotensin converting enzyme inhibitors may affect all of these.

Just as all studies have not demonstrated an improvement in symptoms with ACE inhibitors, nor have they all demonstrated an improvement in exercise performance. Again, most notably those studies that specifically looked at ischaemic heart disease and heart failure have failed to

show consistent benefits. In our study of ischaemic heart disease and angina, we employed 2 exercise protocols. While the longer exercise protocol, which incorporated more gradual increases in speed and incline, showed little difference with and without an ACE inhibitor, the shorter exercise protocol showed a definite reduction in exercise tolerance with an ACE inhibitor. It was notable that, with the shorter exercise protocol, patients were more likely to stop with angina and breathlessness, and that the time to angina was reduced with an ACE inhibitor. During the slower protocol, patients' exercise performance was essentially unaltered, but patients were significant more likely to stop due to angina pectoris while taking captopril. It is possible that induction of sub- clinical (silent) ischaemia may cause a deterioration in ventricular function during exercise in some patients with heart failure and coronary disease which will offset any improvement in central or peripheral haemodynamic or metabolic effects of the ACE inhibitor.

Although one might expect to see improvements in exercise performance in conjunction with a reduction in symptoms, the two need not necessarily go together. Most patients rarely exert themselves above 70% of their maximal capability during daily activity. The patient with heart failure may well restrict his activity such that breathlessness is never really a problem, though he is aware that his capacity for exercise is reduced. A maximal

exercise test, especially when used in conjunction with respiratory gas exchange, is not only useful in determining the patient's maximal effort capacity but also in estimating the "anaerobic threshold". Such measurements give a guide to the level of exercise at which the patient may comfortably exercise for longer periods. Exercise protocols which involve much slower increases in speed and gradient probably more nearly represent the patient's normal daily activity.

It should be emphasized that the exercise test used in these studies was a graded treadmill exercise test. Although exercise performance increased only by a minute or two, this probably obscures a more important improvement as, for the majority of patients, this meant increasing the exercise workload by one stage. On a linear scale, this would represent a more substantial improvement in exercise time.

All exercise protocols involve both subjective and objective components. Other investigators have used tests such as the 6-minute walking test (the maximal distance a patient can walk in a straight line in 6 minutes), and tests which rely on the patient walking a fixed distance.[942] These are very useful when sufficient uncrowded space is available, as it is a more natural form of exercise than treadmill or bicycle exercise. Many patients have great difficulty in co-ordinating their activity during treadmill

exercise, in which case fixed time or distance tests may be the only ones possible. However, space and the requirement for physiological monitoring render treadmill exercise preferable in many cases, Bicycle exercise has advantages over the use of the treadmill as the patient's head and body are held relatively still. This may again be helpful during physiological monitoring. Also, the patient's weight is supported by the saddle during bicycle exercise, perhaps reducing differences between patients of different body mass. However, a relatively small muscle group is exercised, (British) patients are unfamiliar with this sort of exercise, calf fatigue is a more frequent limiting symptom, and maximum oxygen consumption and the likelihood of passing the "anaerobic" threshold are less than with treadmill exercise. These various exercise protocols and modes of exercise should be considered complementary, giving different sorts of information, rather than information which is either worse or better.

CHAPTER 29: ARRHYTHMIAS, HEART FAILURE AND ACE INHIBITORS

INTRODUCTION

The diagnosis of heart failure has long been known to carry a poor prognosis, but the symptoms of heart failure due to valvular disease are now eminently treatable, and the prognosis can be improved by intervention. To date, medical treatment of heart failure primarily due to myocardial failure has been less successful, indicating that accurate diagnosis is necessary for prediction of outcome.

Recent studies and new treatments aimed at reducing morbidity in patients with heart failure have once again highlighted the appalling mortality associated with this condition. There are 3 questions central to the discussion of prognosis in heart failure. Firstly, is it right to prolong life in patients with heart failure? It could be considered that when a patient's symptoms had become of sufficient severity that he may wish to be allowed to die with as little suffering as possible. If there is no effective remedy for the patient's symptoms, it could be argued that it may be "unkind" to prolong his life. Secondly, can we predict those at greatest risk? Thirdly, is there any treatment that will influence prognosis? Effective therapy for symptoms of heart failure could reduce life expectancy or extend it. Therapy other than that required to improve symptoms may be needed to improve prognosis.

SURVIVAL IN HEART FAILURE: THE MODE OF DEATH

In our study of heart failure, we found that 75% of patients died suddenly. This is a greater proportion than reported in other studies but probably represents differences in the mode of reporting.[943] It should be noted that a quarter of the patients in the present study showed progressive deterioration in their heart failure prior to dying suddenly. In many studies of cardiac failure these patients would have been classified as dying of progressive cardiac failure. However, none of them had acute pulmonary oedema immediately prior to death, nor were they noted to be hypotensive for prolonged periods resulting in organ failure. They had required increased treatment to control their symptoms but their final demise was sudden. If the majority of patients die suddenly before reaching "end-stage" heart failure then treatment for prognostic reasons alone is worthwhile.

There is little information on the exact cause of sudden death in patients with heart failure. In patients incidentally undergoing ambulatory ECG monitoring, not necessarily with cardiac failure, the common mode of sudden death has been ventricular tachycardia followed by ventricular fibrillation.[944] In 2 patients who were admitted due to deterioration in their cardiac failure, death occurred during ECG monitoring in our study. Ventricular tachycardia degenerating into ventricular fibrillation was

noted in both cases. Ischaemic heart disease was common in our patients, the risk of death due to sudden deterioration in myocardial function due to myocardial ischaemia or infarction, or due to a pulmonary embolus or a cerebrovascular event, must be relatively high. Indeed, a cardiovascular thromboembolic event was the second most common cause of death in our series. However, the evidence that anti- coagulants alter the incidence of embolic events or overall outcome in heart failure is controversial.[945,946] However, the very low incidence of death due to intractable heart failure should be noted. It is true that we have taken a very rigid definition of death due to heart failure but as this is readily documented, and with adequate guidelines should be reproducible from centre to centre, we strongly advocate that other researchers adopt this definition of heart failure death. With the advent of combined thiazide and loop diuretics, and angiotensin converting enzyme inhibitors, death due to intractable heart failure has become uncommon in my experience. The commonest mode of death in most studies of heart failure is that of sudden death. This is in contrast with the results of the CONSENSUS study from the Scandinavian countries where the majority of patients died from progressive heart failure. However, they chose a group of patient with very severe heart failure and they may well therefore be a self-selected group, very resistant to arrhythmias, producing an abnormal bias towards death due to severe heart failure. Alternatively, as they chose a group of

patients who were already completely immobilised by their heart failure, death may have been ascribed to their heart failure, even though the terminal event was sudden. It is much easier to document the mode of death in patients with milder degrees of cardiac failure where symptoms have been controlled initially. An important feature of the CONSENSUS study was the improvement in functional status as well as in survival. This dual benefit argues strongly that it is right to apply this treatment to patients with severe heart failure.

A report from the Captopril Multi-Centre Research Group has suggested that ACE inhibitors reduce mortality in moderately severe heart failure primarily by reducing the incidence of sudden death.

PROGNOSIS IN CARDIAC FAILURE

The prognosis of cardiac failure is related to the severity of symptoms. Our group of patients with moderately severe heart failure had a 41% mortality after a mean follow-up time of 21 months. Adjusting for the length of follow-up, this gives us approximately a one-year survival of 70% and 2-year survival of 50%. This is in keeping with other studies of patients with similar degrees of heart failure, but notably worse than in a series reporting cases of milder heart failure.[947]

FACTORS PREDICTING PROGNOSIS IN CARDIAC FAILURE

In order of importance, the frequency of ventricular extra-systoles, non-treatment with amiodarone, low mean arterial pressure, and a diagnosis of coronary artery disease, were associated with a poor prognosis, with each of these variables proving extra-predictive information independently of the others. Initial serum potassium concentration and treadmill exercise time also carried further weak but independent prognostic information.

Several other recent studies in populations of patients with heart failure with varying diagnoses have recorded conflicting results regarding the most reliable independent indicators of prognosis.[948-950] Some suggest that ventricular arrhythmias are the most powerful independent indicators[948,951-952] but others have not confirmed this.[950,953-954] It may be that ventricular arrhythmias merely reflect the extent of left ventricular dysfunction.[943,950-951,955] These different views may be a reflection of different study populations with arrhythmias and heart failure caused by idiopathic cardiomyopathy showing a good relation with the extent of left ventricular dysfunction in some studies[956] but not in others.[950] In patients with ischaemic heart disease and left ventricular dysfunction, arrhythmias seem poorly related to the extent of dysfunction.[943,952] Some studies suggest that indices of cardiac function and severity of symptoms are helpful in predicting the prognosis of

patients with heart failure.[946,954,957] Left bundle branch block,[951,958] serum sodium concentration,[949,959] mean arterial pressure,[957] exercise performance,[960] and central venous plasma noradrenaline concentrations[949] have also been found to be useful in some studies. But for each of these indices there are other studies which have not found any predictive value for these variables.[961-963]

The present study clearly demonstrated the frequency of ventricular extra-systoles is strongly associated with a poor prognosis in patients with chronic heart failure caused by left ventricular dysfunction. That death is due to ventricular arrhythmias cannot be proved in a study like this one but the high frequency of sudden death and low frequency of death caused by intractable heart failure suggests that the great majority of deaths in such patients are a result of arrhythmias. The lack of a significant relation between more complex ventricular arrhythmias and mortality may reflect the relatively short period over which the electrocardiogram was recorded. A more protracted period of monitoring may have shown the true frequency of complex arrhythmias.

The present study suggests that arrhythmias are more closely related to functional class and exercise performance than to indices of resting left ventricular performance. Severe ventricular dysfunction was present in the majority of patients in the present study. The lack of

a wide spectrum of cardiac dysfunction would make it difficult to find a relationship with arrhythmias.

Lack of a relationship between prognosis and M-mode echocardiographic measurements of left ventricular function should be interpreted with caution also, especially when comparing different subjects with ventricles that have been damaged by ischaemia. Several studies which have monitored resting haemodynamics invasively also suggest a poor relationship between mechanical dysfunction and prognosis.[946] A relatively poor relationship between exercise performance and left, but perhaps not right, ventricular haemodynamic function, has also been documented.[964,965] The relationship between exercise performance and prognosis may suggest that it is a better overall index of cardiac performance.[960]

Those patients treated with amiodarone appeared to have a better prognosis. The baseline characteristics of those receiving amiodarone differed little from those who did not and significant differences remained in the survival curves, even after correction for confounding variables. Amiodarone appeared to have a particularly strong effect in reducing sudden death, and it is likely that it exerts its beneficial effect through its anti- arrhythmic action. However, amiodarone also has anti- ischaemic effects and it is possible that a reduction of ischaemia-induced arrhythmias occurred.[966,967] This may have implications, not only for those patients with coronary atherosclerosis but

also in patients with congestive cardiomyopathy who may have had sub- endocardial ischaemia without epicardial coronary artery obstruction.[968]

A low mean arterial pressure was also found to be of prognostic significance, as has been noted by others.[957] Plasma renin and catecholamines are known to be inversely related to blood pressure in heart failure,[969] and recent studies have suggested that concentrations of plasma noradrenaline and plasma renin are of prognostic significance in heart failure.[949]Our study also demonstrates the inverse relationship between blood pressure and serum sodium, as would be expected in patients with high concentrations of plasma renin and noradrenaline. Low blood pressure appears also be a marker of clinically more severe heart failure because it is associated with a worse New York Heart Association score and poorer exercise performance.

Patients with coronary artery disease had a poorer prognosis than other diagnostic groups, as in some but not all other studies.[970] The poorer prognosis appears related to sudden death rather than re-infarction. Transient focal ischaemia may have caused arrhythmias, even though angina was not a feature of this study group. The shorter duration of symptoms prior to inclusion in the study, lower mean blood pressure, and lower incidence of arrhythmias in those with coronary artery disease, should also be noted.

The effect of vasodilator agents on prognosis remains controversial, while angiotensin converting enzyme inhibitors appear to have beneficial effects on prognosis.[972,974-975] However, we were unable to demonstrate any effect on overall prognosis associated with the use of either digoxin or angiotensin converting enzyme inhibitors, nor did the dose of diuretic exert any powerful effect. The group treated with ACE inhibitors had worse heart failure however and the statistical analysis may not have compensated for this difference. Certainly, no deterioration in prognosis was noted as in some trials of inotropic agents in patients with heart failure. In our study, the incidence of sudden death was significantly reduced in those on ACE inhibitors; this may have been attributable to the correction of hypokalaemia and hypomagnesaemia and intracellular potassium depletion, beneficial haemodynamic effects, and a reduction in sympathetic nervous activity.[976,977] The statistically insignificant increase in the frequency of vascular events suggests that ACE inhibitors should be used with caution in patients with known critical arterial stenoses. Potential deleterious effects of digoxin and higher doses of diuretics may have been masked by the use of amiodarone and captopril.

THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS ON ARRHYTHMIAS

We have demonstrated in 3 studies that there were reductions in both simple and complex ventricular arrhythmias during treatment with ACE inhibitors in patients with heart failure. This effect does not really constitute an "anti-arrhythmic" effect as the reductions were only of the order of 20-40%. This reduction in cardiac arrhythmias has also been noted by others.[976]

Published animal experimental work is confined to the post-infarction state where experiments in the rat and pig have demonstrated a reduction in re-perfusion arrhythmias.[979,980] However, these effects may not be related to converting enzyme inhibition. There is some evidence that effects differ between ACE inhibitors and also that prostaglandin metabolism may be important in mediating these effects.[979] Captopril, by virtue of its sulphydryl group, may have other effects. The ability of this part of the molecule to act as a proton donor may help to maintain glutathione in the reduced state.[979] This could lead in turn to increased production of endothelium-derived relaxant factor and a reduction in free radical damage. However, the doses of drug given in animal experiments were often many times those that would be administered to man.

Hypokalaemia was more closely related to the frequency of ventricular extrasystoles than has been previously

suggested. Though a causal relationship cannot be confirmed, the association may have been increased by the use of digoxin since hypokalaemia may enhance digoxin binding. In contrast, we were unable to demonstrate an effect of therapeutic concentrations of digoxin on the frequency of arrhythmia, perhaps because of wide inter-individual susceptibility or to a counter- balancing of an improvement in left ventricular function.

The foregoing studies do suggest that ACE inhibitors can alter the QTc interval. As indicated above, it is unnecessary to invoke a primary anti-arrhythmic effect of ACE inhibitors. Angiotensin converting enzyme inhibitors reduce cardiac volumes, cardiac sympathetic activity and angiotensin II, while improving the metabolic profile of the patient and cardiac parasympathetic control. It would be surprising if this constellation of effects did not improve arrhythmias. However, it is not clear which factor, if any, is most important, and may vary from patient to patient. As arrhythmias were also reduced in patients with clear evidence of reversible ischaemia and heart failure despite evidence that ischaemia was not improved, it does suggest that ACE inhibitors do not exert their beneficial effect on arrhythmias by preventing focal ischaemia. It is still possible that ACE inhibitors may improve myocardial perfusion in a more subtle fashion.

The demonstration of improvement in "simple" arrhythmias is

not sufficient. Evidence of a reduction in malignant arrhythmias such as sustained ventricular tachycardia and the incidence of sudden death is required before anti-arrhythmic action can be deemed clinically useful. It is possible that on-going studies into the effects of ACE inhibitors will clarify the importance of this reduction in arrhythmias.

THE EFFECT OF TREATMENT ON PROGNOSIS

As we have noted above, the CONSENSUS study demonstrated a reduction in death due to progressive heart failure. This is an important finding but I have argued that it may not be relevant to the majority of patients with heart failure. The reasons why ACE inhibitors retard the progress of heart failure is unclear. Simple reduction in preload and afterload could reduce cardiac volumes and improve cardiac function. Alternatively, levels of angiotensin II sufficient to cause myocyte necrosis in animal experiments may be found in patients with heart failure.[981] Reduction of the direct toxic effects of angiotensin II on myocytes could preserve cardiac function. We have also noted very high circulating levels of noradrenaline in some patients which could potentiate myocyte damage also.[982,983] Beneficial effects of ACE inhibitors on free radical- mediated damage and on the intercellular matrix are also theoretically possible.[984] Therefore, there are good reasons why ACE inhibitors could retard progression of heart failure. In patients with less severe heart failure, the Captopril

Multi-Centre study reported retrospectively a reduction in sudden death.[985] Though this requires confirmation it does imply that therapy to improve symptoms in patients with moderate heart failure may also favourably affect prognosis. Sudden death could be prevented by favourable effects of ACE inhibitors on arrhythmias or preservation of myocardial blood flow. Preservation of cardiac function is likely to be important also. The present study suggests that amiodarone may specifically reduce the incidence of sudden death. Though this awaits confirmation, it does suggest that arrhythmias may be an important cause of sudden death.

In contrast, class I anti-arrhythmic agents appear to be contra-indicated in patients with heart failure. A retrospective study of procainamide failed to show any benefit. The CAST study incorporated many patients who had evidence of heart failure and ventricular ectopy.[986] Patients receiving active therapy had a worse outcome than those receiving placebo. Class I anti-arrhythmic agents appear to suppress arrhythmia less effectively in the presence of severe left ventricular dysfunction and have more pro-arrhythmic effects.[987,988] Class I anti- arrhythmic agents also have deleterious haemodynamic effects.

Agents such as beta-blockers and verapamil also have negative inotropic effects and are generally unsuitable in patients with heart failure, although there is conflicting

evidence of benefit with beta-blockers.

Agents that alter beta-adrenergic tone, such as xamoterol, also have the potential to adversely affect prognosis, at least in patients with severe heart failure. Though xamoterol may improve heart function in milder heart failure, in patients with severe heart failure and very high levels of sympathetic activity a decline in ventricular function may be observed.

Though diuretics have been implicated in the neuroendocrine and metabolic disturbance associated with heart failure, there is no direct evidence linking them to a worse prognosis. Obviously, in patients with acute pulmonary oedema they may be life-saving, while in the patient who is over-treated they are going to be deleterious. However, as patients with worse heart failure will require more diuretic and have a worse prognosis, it is difficult to implicate directly diuretic therapy in the prognosis of heart failure.

The advent of implantable defibrillators has given a further mode of arrhythmia treatment in patients with heart failure. Preliminary evidence does suggest that in patients with poor ventricular function and a high incidence of ventricular arrhythmia such devices may improve prognosis.[989] This implies that control of arrhythmias is important but that proper selection of the patients and the therapeutic

agent is required. The criteria for such selection remain to be established.

SUMMARY

Angiotensin-converting enzyme inhibitors have a beneficial effect on survival in patients with heart failure, which is probably partly due to a reduction in sudden death. This is in contrast to class I anti- arrhythmic agents which have more potent anti-arrhythmic effects but depression cardiac function. However, improving cardiac function alone may not be protective, as increased mortality due to inotropic therapy has been reported. Beneficial effects on arrhythmias, albeit small, associated with improved cardiac function, improved autonomic control and correction of potassium depletion, are all likely to play a role in the observed benefit with angiotensin converting enzyme inhibitors.

CHAPTER 30: ACE INHIBITORS IN ISCHAEMIC HEART DISEASE

It has been established beyond reasonable doubt over the last 6 years that ACE inhibitors improve symptoms, exercise performance and haemodynamics in patients with moderate or severe heart failure. The CONSENSUS study demonstrated that ACE inhibitors could not only reduce mortality in patients with very severe heart failure but also retard or prevent progression of the condition. Some have argued that if ACE inhibitors prevent progression of heart failure in severe cases then it may also do this in cases of mild heart failure. This has generated much speculation over a role for ACE inhibitors in mild heart failure or asymptomatic left ventricular dysfunction. An increasing number of these are likely to have angina pectoris as the dominant symptom.

What then is the role of ACE inhibitors in the management of ischaemic heart disease? The answer is distinctly beneficial for some syndromes, ineffective for others, and possibly harmful for some.

The role of ACE inhibitors in ischaemic heart disease may be considered under the following headings:

1) **Chronic heart failure**
2) **Stable angina**
3) **Unstable angina**
4) **Acute myocardial infarction**
5) **Cardiogenic shock**

CHRONIC HEART FAILURE

The majority of patients included in studies of chronic heart failure have coronary artery disease as the basis for their myocardial dysfunction. It is therefore highly probable that the majority of patients with heart failure due to ischaemic heart disease benefit from ACE inhibitors. However, not all studies show benefit with ACE inhibitors in heart failure, and it may be that some patients, possibly those with additional reversible ischaemia due to epicardial artery disease, fail to improve.

ANGINA

Daly first demonstrated an anti-anginal effect of ACE inhibitors in a study using single doses of captopril in patients with high blood pressure and angina.[990] A further recent study has also suggested an anti-anginal effect of captopril in patients with angina and hypertension after medium- to long-term therapy.[991] However, a series of studies investigating the possible anti-anginal effects of ACE inhibitors in patients with angina but without marked hypertension failed to show any difference from placebo.[992-995] The present study, comparing placebo and captopril in patients with heart failure and angina treated with diuretics, suggested that captopril may actually exacerbate the symptoms of angina and increase nitrate consumption. Exercise performance was reduced in this

study, thus increased mobility did not account for the deterioration in symptoms.

How then do we account for the disparity of the effect of ACE inhibitors in these 3 groups of patients? Theoretically, ACE inhibitors could alter anginal symptoms in a number of ways.

Potential Effects on Myocardial Oxygen Demand

In patients with heart failure, ACE inhibitors reduce the resting heart rate but they have no marked effect on exercise heart rate. Therefore, they are unlikely to alter the ischaemic threshold by this mechanism.

A reduction in afterload could also reduce myocardial oxygen consumption by lowering the systolic wall tension and therefore stroke work and cardiac efficiency. Potentially, patients with hypertension have most to gain by this mechanism, though patients with heart failure and an elevated systemic vascular resistance could also benefit.

A decrease in preload may decrease myocardial oxygen demand by decreasing diastolic wall tension. Importantly, in the dilated ventricle, even in the absence of obstructive epicardial coronary artery disease, an increase in preload may cause subendocardial ischaemia. It is well known that

the balance between myocardial oxygen supply and demand is precarious in the failing heart. I have demonstrated that captopril and enalapril can reduce ventricular dimensions in patients with heart failure and that this is accompanied by a decrease in preload.

Myocardial oxygen consumption could also be reduced by reducing myocardial contractility. An anti-ischaemic effect of ACE inhibitors by this mechanism is not generally recognised and, indeed, might be considered unfortunate by some. However, angiotension II does have positive inotropic effects, though these are largely obscured by the concomitant increase in afterload as a result of arterial constriction. Angiotensin converting enzyme inhibitors, by reducing angiotensin II levels, could have a mild negative inotropic effect. There is a further mechanism by which ACE inhibitors could reduce the inotropic state of the ventricle. It has been demonstrated both in patients with heart failure and hypertension that ACE inhibitors can reduce the concentration of noradrenaline in the coronary sinus, suggesting that ACE inhibitors reduce cardiac sympathetic activity.[998]

There are multiple reasons why ACE inhibitors can and probably do reduce myocardial oxygen demand. However, in the present study angina frequency and GTN consumption increased. This was not due to an increase in patient activity as the maximal achieved oxygen consumption and

exercise performance deteriorated, with angina more frequently limiting exercise during the "slow" test.

Myocardial Oxygen Supply

Angiotensin II, anti-diuretic hormone, and increased sympathetic activity may increase coronary artery tone in heart failure.[996] Angiotensin converting enzyme inhibitors have been infused into the coronary artery and this results in coronary vasodilatation and an increase in coronary blood flow.[997-1002] However, in studies where ACE inhibitors have been administered systemically, the fall in coronary vascular resistance is counter-balanced by a reduction in perfussion pressure, resulting in little change in coronary blood flow. Most of these studies have been conducted in the supine position. As it is likely that coronary perfusion pressure falls in the upright position, coronary blood flow may also fall. However, the effect of ACE inhibitors on coronary blood flow are even more complex. Angiotensin converting enzyme inhibitors reduce cardiac sympathetic activity which could reduce coronary artery tone. Coronary blood flow is closely matched to myocardial oxygen requirements leading to auto-regulatory changes in coronary tone. A reduction in afterload and preload could then lead to an appropriate fall which is economically desirable. Angiotensin II also appears to have differential effects upon large and small coronary arteries, the constrictor effect being sustained on the large conductance vessels but undergoing tachyphylaxis in the small distal

vessels and perhaps the coronary collateral supply. This is the converse of the effect of nitrates.[1003,1004] Suppression of angiotensin II in this situation could cause a coronary "steal" effect.

It should always be remembered that angina is rarely a problem of global myocardial oxygen supply and that focal ischaemia is the rule rather than the exception.

Clinical Studies of Angina and ACE Inhibitors

There are now many studies investigating the effects of ACE inhibitors in angina. In general, those studies which have reported the effects on exercise-induced angina or pacing-induced angina in the supine position, usually with single doses of an ACE inhibitor, have reported some improvement.[1004,1005] There are now 6 studies which have investigated the effect of multiple dose ACE inhibitors on exercise-induced angina in the upright position. In 4 studies, patients with angina as the sole complaint were studied, and none of these studies demonstrated significant benefit with an ACE inhibitor.[992-995] One study in patients with hypertension and angina has suggested significant improvement.[991] The present study in patients with angina and heart failure has suggested a significant deterioration in angina. At first sight it may be difficult to reconcile the differences but the key is probably the effects on coronary perfusion pressure. In hypertensive patients, a reduction in cardiac loading conditions may reduce myocardial oxygen

requirements without an undue reduction in coronary perfusion pressure. In normotensive subjects with angina the effects of reducing coronary perfusion pressure are probably balanced by the reduction in myocardial oxygen demand. In heart failure, the marked reduction in coronary perfusion pressure with the combination of diuretics and ACE inhibitors, may lead to deterioration. This is especially likely to occur if coronary stenosis is present in an artery supplying myocardium with a relatively normal function.

UNSTABLE ANGINA

I am unaware of formal studies in this field and would recommend caution. The patient with hypertension and unstable angina would be most likely to benefit both theoretically and on the scanty evidence available.

ACUTE MYOCARDIAL INFARCTION

Myocardial infarction leads to an acute activation of the sympathetic nervous system, the renin-angiotensin system, and anti-diuretic hormone. In patients sustaining a large myocardial infarction sustained increases are seen.

Animal work in this area has suggested that ACE inhibitors may reduce myocardial damage occurring as a result of coronary artery occlusion and re- perfusion.[1006-1009] Apart

from the reduction in myocardial oxygen demand due to altered loading conditions, there are 4 proposed beneficial mechanisms. Firstly, ACE inhibitors in general may reduce cardiac sympathetic overflow which could be protective. However, captopril, by virtue of its sulphydryl group, could have additional protective effects. The attached sulphydryl group may scavenge free radicals which are felt to cause myocardial damage at the time of re- perfusion. The sulphydryl group may also maintain or enhance the production of endothelial-dependent relaxing factor. Angiotensin converting enzyme inhibitors could also have a role in preventing coronary stenosis occurring at the site of plaque rupture by preventing smooth muscle proliferation. Angiotensin converting enzyme inhibitors may also cause accumulation of bradykinin by inhibiting its catabolism, which in turn may have cardio-protective effects.

Initial animal work has indicated beneficial effects of ACE inhibitors, in particular, captopril, on post- infarction myocardial dysfunction and mortality. Human studies have been conducted in patients with acute myocardial infarction to determine if captopril could reduce the severity of re-perfusion damage when used in conjunction with thrombolytic therapy.[1010] In some centres this was associated with worrying hypotension. However, these initial studies used relatively high doses of intravenous captopril. McAlpine et al used smaller oral doses of captopril (3.125

mg titrated up over a period of hours to 12.5 mg)[1011] This resulted in beneficial haemodynamic effects and a significant suppression of angiotensin II, even with the smallest dose of captopril. Severe hypotension did not occur. Another study (Di Pasquale - personal communication) demonstrated that captopril could reduce the frequency of complex ventricular arrhythmias after myocardial infarction. Others have suggested that an acute reduction in plasma noradrenaline may indicate a beneficial effect of ACE inhibitors as the concentration of noradrenaline in plasma has been related to prognosis after myocardial infarction.

Longer-term controlled studies have initiated ACE inhibitors some days or weeks after myocardial infarction. These have generally shown a small but significant reduction in cardiac volume. It is still unclear whether this represents purely a haemodynamic effect of continued ACE inhibition or genuine ventricular remodelling. Studies are awaited to determine if the effects on ventricular function can still be seen one or more months after withdrawal of the ACE inhibitor. More recently, Lamas and co-workers[1013] have demonstrated that in patients who had a moderately severe myocardial infarction, exercise tolerance deteriorates in the post-infarction period. In a double-blind placebo-controlled study, they demonstrated that this could be prevented by introduction of captopril. While changes in ventricular volumes are of interest to the

cardiologist, this latter aspect may have more relevance for the patient. However, it is far too early to generally recommend ACE inhibitors in the immediate post-infarction period or, indeed, for asymptomatic ventricular dysfunction. The outcome of large, multi-centre controlled studies such as SOLVD (Study on Left Ventricular Dysfunction) and SAVE (Survival and Ventricular Enlargement) may give us more information on how important this aspect of therapy is.

Animal experimental work has demonstrated that ACE inhibitors can reduce the severity and duration of ventricular arrhythmias during coronary re-perfusion.[1006] Again, there is a suggestion that there may be differences between ACE inhibitors, with an additional role for the sulphydryl group. However, other studies comparing ramipril and captopril in rats have suggested a reduction in ventricular fibrillation only with the former. Perhaps the differences occurred only by chance. Perhaps it is suggested that animal models of myocardial infarction are highly operator- dependent.[1014]

CARDIOGENIC SHOCK

Lipkin reported 3 patients suffering from cardiogenic shock who were subsequently administered captopril.[1015] Administration of captopril, starting at a dose of 1 mg and gradually increasing to 6.25 mg, resulted in a favourable haemodynamic response, with a fall in left ventricular filling pressures, a rise in cardiac output and urine flow, with the maintenance of arterial pressure. Although these preliminary results are optimistic, wider experience is required before the use of ACE inhibitors can be generally recommended in this condition. It is imperative that left ventricular filling pressures are documented for proper management of these patients. Only those with a marked elevation in left ventricular filling pressure are likely to benefit from an ACE inhibitor.

CONCLUSIONS

The ideal anti-anginal agent with which to treat patients with heart failure and angina is yet to be discovered. Amiodarone, diltiazem, nicardipine, xamoterol, and nitrates all have their advocates. Calcium antagonists and converting enzyme inhibitors often produce marked hypotension when used in combination in patients with heart failure and are to be used with great caution. Xamoterol may be very useful as long as the heart failure is not too severe. Amiodarone, by reducing the frequency of ventricular arrhythmias and its marked anti-anginal

potency, must be considered one of the best drugs in this situation. In moderate doses, side-effects, even over prolonged periods of time, are few. Nitrates may be useful but tolerance is a problem, even in the patient with heart failure.

When contemplating the use of ACE inhibitors in ischaemic heart disease the first problem is to define the question more precisely. Many treatments for myocardial infarction are inappropriate for the management of angina, and many treatments for angina are inappropriate for heart failure. There is little doubt that ACE inhibitors have had a major beneficial impact upon heart failure induced by coronary artery disease. The treatment of acute myocardial infarction with ACE inhibitors is a current area of research but cannot be recommended clinically yet. For patients with angina, ACE inhibitors do seem to have some beneficial effects in hypertensive patients but they do not appear to reduce the severity of angina in normotensive patients or patients with heart failure. However, the patient with heart failure and angina may still benefit from the introduction of an ACE inhibitor. The present study suggests that the frequency of ventricular arrhythmias may be reduced and there is always the possibility, still theoretical, that progressive ventricular dysfunction may be ameliorated.

CHAPTER 31: CONCLUSION

The idea of vasodilator therapy for heart failure has been toyed with for almost one hundred years, possibly more. The results were largely disappointing, either because tolerance occurred to the vasodilator actions of the drugs, or because vasodilatation is an ineffective mode of treatment for chronic heart failure. This all appeared to change with the discovery that angiotensin converting enzyme inhibitors were effective in the treatment of chronic heart failure, or so it might seem.

However, activation of the renin-angiotensin system in heart failure indicates not only a haemodynamic disturbance but also profound metabolic disturbances throughout the body. Moreover, the renin-angiotensin system has secondary effects on the sympathetic and parasympathetic nervous systems that may have consequences not only for vascular resistance and cardiac function but also heart rhythm control.

Angiotensin converting enzyme inhibitors are able to reverse or ameliorate many of the endocrine, neural and metabolic consequences associated with renin-angiotensin system activation in heart failure and improve prognosis. It is likely that these effects make a significant contribution to the benefits of angiotensin converting enzyme inhibition. Indeed, as drugs with more profound haemodynamic effects have made little impact in the management of heart failure, the metabolic effects may be of greater importance.

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