THE ROLE OF NEUROHUMORAL SYSTEMS IN THE PATHOPHYSIOLOGY AND MANAGEMENT OF HEART FAILURE

BY

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THIS THESIS IS DEDICATED

TO MY WIFE,

CAROLYN.

CONTENTS:

Chapter 3: ASSESSMENT OF SEVERITY OF HEART FAILURE AND THE RESPONSE TO THERAPY

Chapter 4: MEASUREMENT OF HAEMODYNAMIC PARAMETERS

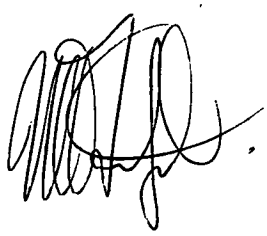
Chapter 5: HORMONE ASSAYS AND METABOLIC BALANCE

WORK DONE PERSONALLY:

I was involved in the design of the protocol for each investigation and I selected the patients involved in these studies, explained in detail the nature of each study, and obtained informed, written consent. All catheters were inserted by me, and I was available at all times to attend the patients during their hospital stay in the event of problems arising. I routinely checked on their physical well-being at least daily while they were in hospital. After discharge, I saw all patients for follow-up care at a special "Heart Failure" clinic.

All exercise tests were supervised by me, and I performed all radionuclide angiographic studies using the "Nuclear Stethoscope". I was present on every occasion when blood sampling and haemodynamic measurements were made, except when arrangements for cover were made with Dr. Nicholls or Dr. Ikram (which occurred infrequently). A cardiology technician was present at most measurement times and calculated results which were checked by me on a weekly basis. I tabled the primary data and performed statistical analyses. All figures were initially drawn by myself then copied and photographed by the Dept. of Medical Illustrations. The investigations were performed over the last three years, while I was employed as Registrar, and later as Senior Registrar in Cardiology at the Princess Margaret Hospital, Christchurch.

This thesis contains no material which has been accepted for the award of any other degree or graduate diploma in any university. It contains no material previously published or written by another person, except when due reference has been made in the text of this thesis.



M. A. Fitzpatrick

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I wish to thank the nursing staff of the PMH Theatre Recovery Ward who cared very diligently for our patients while they underwent investigation. Without this care, none of the first three studies to be reported would have been possible. I also wish to thank the dieticians for carefully preparing meals for metabolic balance studies, and the Special Test Sisters who collected and stored most blood samples. The staff of the Pathology and Endocrinology laboratories patiently taught me the basic techniques for assaying hormones and electrolytes.

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The manuscript for each study reported in this thesis was prepared initially for publication in the Medical Literature. I am most grateful for the constructive criticism and advice provided by Professor Espiner, and Dr. Nicholls and Dr. Ikram in the preparation of these manuscripts.

ABSTRACT:

CHAPTER 1:

Congestive heart failure is a common and lethal disorder. Improved understanding of the pathophysiology has led in recent years to more rational therapeutic regimes. The historical development of modern concepts of the pathophysiology and management of heart failure are outlined, concentrating mainly on the role of neurohumoral systems - the renin-angiotensin-aldosterone system and sympathetic nervous system. Deficiencies in current knowledge are discussed, from which I outline the objectives of the studies presented in this thesis.

CHAPTER 2:

Only those patients with documented left ventricular dysfunction were included in the studies. In this chapter, I outline methods of patient selection: referral; definition of heart failure and aetiology; and finally, inclusion and exclusion criteria. Ethical guidelines followed implicitly in the studies are then outlined.

CHAPTER 3:

Current methods of assessment of the severity of heart failure and underlying left ventricular dysfunction are reviewed. Emphasis is placed on those methods used in this thesis: NYHA Functional Classification; invasive haemodynamics; radionuclide angiography; echocardiography; and exercise testing.

CHAPTER 4:

This chapter is concerned with methodology for measuring haemodynamic parameters: intra-cardiac pressure, cardiac output, and forearm blood flow.

CHAPTER 5:

Correlation of hormone and haemodynamic measurements in heart failure under control conditions and following therapeutic intervention forms the basis of three studies reported in this thesis. In this chapter, I briefly outline assay methods used in our laboratory. Metabolic balance was instituted to facilitate the interpretation of hormone levels in the studies. Methods for performing these metabolic studies are dealt with in this section.

CHAPTER 6:

In this study, I document the acute haemodynamic, hormone, and electrolyte response to enalapril in heart failure, and correlate these changes with the short-term clinical response. Enalapril appears to be a long-acting angiotensin converting enzyme inhibitor that effectively reduces elevated angiotensin II levels found in heart failure. The greatest haemodynamic improvement occurred in those patients with the highest baseline angiotensin II levels. Over a period of 4 to 8 weeks, exercise capacity improved in those patients who were most severely afflicted, on higher frusemide doses, with the greatest activation of the renin-angiotensin-aldosterone system.

CHAPTER 7:

The haemodynamic, hormone and electrolyte effects of prenalterol infusion were documented in a similar fashion to the previous study. I confirmed the positive inotropic action of this drug, a selective beta-1 receptor agonist. The drug is available in an oral form, thus it may have a place in the long-term management of heart failure, but this will depend on whether or not the acute haemodynamic response is sustained long-term. Prenalterol activated the renin-angiotensin system, presumably by direct beta-1 stimulation of the juxta-glomerular apparatus. This did not appear to have haemodynamic effects in the short-term, however it may ultimately prove to be detrimental during long-term therapy.

CHAPTER 8:

I retrospectively analysed the control data from the preceeding two studies and an earlier study performed in our unit (Maslowski et al, 1981a). Cardiac catheterisation appears to significantly influence cardiac and hormone parameters for a period of up to twelve to eighteen hours. Thereafter, these parameters are relatively stable and more truly represent "baseline" levels, from which haemodynamic-hormone relationships and the effects of therapeutic intervention can be more accurately assessed. Activation of the renin-angiotensin-aldosterone system depends largely on the severity of underlying myocardial dysfunction and frusemide dosage, while the sympathetic nervous system appears to play a lesser role in determining cardiac function at rest.

CHAPTER 9:

This study was the first double-blind, placebo controlled trial to investigate the effects of beta-blockade in dilated cardiomyopathy. I refute the claims of Swedish workers for therapeutic benefit in this condition, claims which are contrary to our current notions concerning the role of the sympathetic nervous system in heart failure, and the administration of beta-blocking agents in this syndrome.

CHAPTER 10:

In this double-blind, controlled study I document haemodynamic deterioration associated with diminished exercise capacity following withdrawal of long-term captopril therapy for heart failure. This confirms the sustained effectiveness of angiotensin-converting enzyme inhibitors in the long-term management of heart failure.

CHAPTER 11:

The major findings of the above studies are summarised.

CONTRIBUTION TO THE SCIENTIFIC AND MEDICAL MILIEU:

The studies embodied in this thesis contribute significantly to knowledge concerning the role of neurohumoral systems in the pathophysiology and management of heart failure. The following publications (excluding abstracts) have or will appear in the medical literature:

1. Double-Blind Trial of Chronic Oral Beta-Blockade in Congestive Cardiomyopathy.
   Lancet ii:490-3, 1981.

2. Beta-Blockade for Dilated Cardiomyopathy: the Evidence Against Therapeutic Benefit.
   Eur Ht J 4(A):179-80, 1983.

3. Haemodynamic, Hormonal and Electrolyte Effects of Prenalterol Infusion in Heart Failure.
   Circulation 67:613-9, 1983.

4. Haemodynamic, Hormonal and Electrolyte Effects of Enalapril in Heart Failure.
   Br Ht J (in press).

5. Acute Haemodynamic, Hormonal, and Electrolyte Effects and Short-term Clinical Response to Enalapril in Heart Failure.
   J Hypertension (in press).

6. Stability of Haemodynamic and Hormonal Parameters, and Their Inter-relationships in Heart Failure.
   To be submitted to J Clin Sci.

7. Withdrawal of Long-term Captopril Therapy for Heart Failure: A One-month, double-blind controlled trial.
   To be submitted to Lancet.

So far, data from the studies in this thesis have been presented at the following international meetings:

1. 54th Annual Scientific Session of the American Heart Association, Dallas, Nov, 1981 (Ch 9).

2. 30th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand, Canberra, May, 1982 (Ch 7).

3. Symposium on "The Failing Myocardium - What we have learned since Withering", Salzburg, June, 1982 (Ch 9).

4. 9th World Congress of Cardiology, Moscow, June, 1982 (Ch 7).

5. 32nd Annual Scientific Session of the American College of Cardiology, New Orleans, March, 1983 (Ch 6).

6. 8th Asian-Pacific Congress of Cardiology, Nov, 1983 (Ch 10).

CHAPTER 1

INTRODUCTION

" Heart failure, the consequence of many forms of heart disease, is one of the most common and serious disorders that afflicts individuals of all ages"

Braunwald (1981)

1.1 HEART FAILURE - THE PROBLEM:

Congestive heart failure is a very common clinical problem which leads to incapacitating symptoms and often progresses to the point of refractoriness to therapy. From the time of diagnosis, mortality over the following five years is about 50% (McKee et al, 1971). In more severe cases, characterised by marked haemodynamic abnormalities, the mortality rate may be even higher (Fuster et al, 1981). While initial therapy produces symptomatic relief in many patients early in the course, progressive worsening of symptoms with time is the usual outcome, although sudden death may intervene.

In the last three decades, cardiology has benefited from extensive research efforts. With application of this knowledge, we have witnessed more than a 25% decline in age-corrected mortality from ischaemic heart disease and a 37% decrease in stroke mortality (Fromer 1982). Furthermore, there has been dramatic progress in our ability to manage most major types of cardiovascular disease (coronary artery disease, arrhythmias, valve and congenital heart diseases and hypertension).

In contrast to these advances our ability to manage major derangements of heart muscle function has made very little progress. Thus, heart failure is now the leading pathophysiological mechanism of death from heart disease in the hospital setting (Fromer, 1982).

Despite the prevalence of the syndrome, there has been a remarkable lack of information regarding:

1. Prognosis and mode of death;
2. Mechanisms of progression of the syndrome;
3. Timing of therapeutic intervention; and
4. Assessment of severity and therapeutic benefit with regard to symptoms, and life-expectancy.

Part of the problem lies in the heterogeneous nature of the syndrome, which may arise from any form of heart disease, and from imprecision in making a definitive diagnosis and evaluating its severity, which are likely to be a strong factors in determining prognosis. In the few studies where adequate definitive diagnosis has been made (Bruschke et al, 1973; Fuster et al, 1981), the prognosis in the presence of heart failure is poor and in many cases is worse than that for many forms of malignancy (McKee et al, 1971).

Traditional therapy involves exercise curtailment, salt restriction and administration of digitalis and diuretics, however many patients fail to respond or respond poorly. New therapeutic modalities (vasodilators, blockade of the renin-angiotensin-aldosterone system and non-glycoside inotropes) show promise, making management of heart failure one of the most rapidly expanding areas of cardiac therapeutics (Braunwald, 1982).

In recent years, increasing attention has been devoted to the neurohumoral vasoconstrictor, and dilator systems which contribute to fluid retention, increase heart rate and alter regional blood flow. These systems include:

1. The Renin-Angiotensin-Aldosterone system;
2. The Sympathetic Nervous System;
3. Antidiuretic hormone;
4. Kinins;
5. Prostaglandins;

Alterations in the activity of these vasoactive systems increase ventricular afterload, thereby increasing left ventricular work and ultimately potentiating heart failure (see section 1.7).

The causes and consequences of these disturbed mechanisms are not well understood (Braunwald, 1982). Reversal of the increased ventricular afterload observed in heart failure is beneficial (Franciosa, 1981), however "tolerance" to some vasodilators has been attributed to activation of those neurohumoral constrictor systems not initially blocked (Colucci et al, 1980b). Furthermore, tolerance to inotropic therapy may occur for similar reasons.

The studies embodied in this thesis contribute significantly to the growing fund of knowledge concerning the role of these neurohumoral systems in the manifestations of heart failure and its therapy. Before describing these studies in detail, it is pertinent to review briefly the historical development of concepts in heart failure, its manifestations and pathophysiology. Current knowledge concerning the role of the neurohumoral systems in heart failure will then be outlined with emphasis being placed on those areas under investigation, namely the renin-angiotensin-aldosterone system, the sympathetic nervous system, and antidiuretic hormone (ADH).

1.2 HISTORICAL PERSPECTIVES: (Jarcho 1980 & Braunwald 1981)

The principal clinical manifestations of heart failure, dyspnoea and oedema, were recognised in antiquity, although heart failure as an entity could not be described until the fundamental function of the circulation had been identified. The Greeks and Romans attributed dyspnoea and oedema to an obstruction of the upper airways, and to an abnormality of the urinary system respectively.

William Harvey (1578-1657), despite his monumental contribution to cardiac physiology and his lifelong involvement in the practice of medicine, did not write about disorders of the organ whose function he had described. In his book "De Corde" (1669), Richard Lower pointed out that it is necessary for the two sides of the heart to have similar strengths to maintain the circulation. He appreciated that inequality of the two sides could lead to symptoms, and he presaged much later work on heart failure by pointing out that the cardiac parenchyma may be subject "to various illnesses and inflammation", which could interfere with its "pulsations", leading to a feeble cardiac output. In this manner, the concept of what we now call "forward heart failure" was first formulated.

Almost simultaneously, in Italy, Marcello Malpighi (1628-94) expressed the belief that dyspnoea was the result of a "heaviness of the lungs caused by retarded circulation in the pulmonary vessels" - a predecessor of the "backward failure" concept. In 1832, James Hope championed this theory, contending that when heart failure occurs one or the other ventricle fails to discharge its contents normally and the pressures and volumes in the atrium and venous system behind the failing ventricle become elevated.

A current formulation of this concept would suggest that the inability of cardiac muscle to shorten against a load alters the relationship between ventricular pressure and volume, so that end-systolic volume rises. The following sequence of adaptations then occurs:

1. ventricular end-diastolic volume and pressure increases;
2. pressure rises in the venous and capillary beds;
3. transudation occurs;
4. extracellular volume icreases.

Although these adaptations at first tend to maintain normal cardiac output, many of the symptoms that are characteristic of heart failure result directly from this sequence of fluid sequestration in the interstitial spaces of the lungs, liver, subcutaneous tissues, and serous cavities.

In contrast to the "backward theory", proponents of the "forward failure theory" expounded most clearly by MacKenzie in 1913, maintain that the clinical manifestations of heart failure result directly from an inadequate discharge of blood into the arterial system. According to this formulation, the principal clinical manifestations of heart failure arise from reduced cardiac output, which results in diminished perfusion of vital organs including: the brain, leading to mental confusion; the skeletal muscles, leading to weakness; and the kidneys, leading to sodium and water retention. Although these two seemingly opposing views concerning the pathogenesis of heart failure led to lively controversy during the first half of the century, a rigid distinction between backward and forward heart failure now seems artificial, since both mechanisms appear to operate to varying extents in most patients with heart failure.

Schroeder (1941) first documented the vital role of sodium restriction in the treatment of heart failure. This led to the realisation that sodium retention (rather than water retention) by the kidneys was the primary mechanism by which fluid was retained in patients with heart failure (Futcher & Schroeder, 1942). The importance of enhanced tubular reabsorption in the diminished

urinary excretion of sodium was suggested by Schrodeder (1941), and later confirmed (Urquhart & Davis, 1963).

It was not until Parrish (1949) and Deming & Luetscher (1950) reported increased sodium-retaining activity in the urine from patients with heart failure, that the possibility of hormone-induced renal sodium retention received scientific support. Davis et al (1956) and Singer (1957) confirmed that this active material was aldosterone when they demonstrated increased levels of this substance in urine and adrenal vein blood respectively. Davis et al (1962) subsequently suggested that increased circulating angiotensin II levels were responsible for hypersecretion of aldosterone in experimental heart failure.

The manifestations of heart failure are now thought to be largely due to a disturbance of feed-back control of fluid homeostasis in response to a change in renal perfusion (forward failure), in association with redistribution of blood flow by neurohumoral reflexes (Hamer, 1982 - p.1). Congestive heart failure appears when a cardiac output necessary for tissue needs cannot be produced by the diseased heart using compensatory mechanisms of the sympathetic nervous system, which include:

1. tachycardia;
2. ventricular hypertrophy (Strobeck & Sonnenblick, 1981);
3. moving to a higher ventricular function curve (Sarnoff & Beglund, 1954) so that compensation is attempted through the Starling response.

The last factor is aided by renal sodium and water retention. The retained fluid is distributed by the venous system to provide suitable filling pressures in each ventricle to maintain an adequate cardiac output (Guyton, 1963), however, this fluid cannot be retained in the intravascular compartment. Sequestration in the interstitial spaces results in the appearance of oedema.

Modern diuretic therapy has undoubtedly enabled many patients with cardiac decompensation to survive in an oedema-free state for longer periods (Mudge, 1980). Thus, the full blown syndrome of

congestive heart failure is seen less frequently. Patients are more often troubled by symptoms related to diminished cardiac output, namely fatigue and reduced exercise capacity. As a result, greater research emphasis is now being directed toward agents that can improve cardiac output by direct inotropic action or blockade of neurohumoral vasoconstrictor systems that adversely effect the regional distribution of blood flow in heart failure.

The investigations in this thesis are concerned largely with the neurohumoral changes that are involved in altered regional blood flow and sodium retention in heart failure, and in particular, with the effect of diuretics, vasodilators and inotropic agents on these systems. Renal changes will only be outlined briefly in the next section because they are not directly related to this thesis. The brevity of this section, however, does not belie the central role that the kidney plays in the salt and water retention.

1.3 THE KIDNEY IN HEART FAILURE:

Salt and water retention by the kidney is a major compensatory adjustment brought about in an attempt to restore the effectiveness of the circulation (Braunwald et al, 1965). Although the quantitative role of each mechanism has not been clarified, there are at least five mechanisms which have been proposed in heart failure:

1. Renal Haemodynamic changes:

Renal haemodynamic changes are currently thought to play the major role in sodium and water retention in heart failure (Hume et al, 1978). A decline in renal blood flow and plasma flow is commonly observed (Merrill, 1949 & Mokotoff et al, 1948), but this is associated with little or no change in glomerular filtration rate (Heller & Johnson, 1950). As a result of this, a rise in filtration fraction is consistently found in heart failure (Vander et al, 1958). The mechanisms by which diminished sodium excretion results from these haemodynamic alterations are detailed elsewhere (Hume et al, 1978), and as they are not pertinent to this thesis, they will not be discussed further.

2. Aldosterone:

Aldosterone contributes to sodium retention by enhancing distal sodium reabsorption in exchange for potassium. Its role in heart failure will be discussed further in the next section.

3. "Third Factor":

The existence of an unidentified "salt-losing hormone" (third factor), probably of cerebral origin, that may inhibit tubular sodium absorption as the extracellular fluid expands, has been postulated (Schrier and de Wardener, 1971; Grekin et al, 1979).

A disturbance of such a mechanism could contribute to the sodium retention seen in heart failure.

4. Intra-Renal Redistribution of Blood Flow:

Alterations in the distribution of blood flow within the kidney (Kilcoyne et al, 1971) occur as part of the response to the general reduction in renal blood flow; the tendency to medullary, rather than cortical blood flow may favour nephrons with more potent sodium-retaining properties. A local intrarenal effect of renin may play a part here (Levens et al, 1981).

There are two populations of nephrons in the kidney (Britton, 1981):

1. a cortical group with a juxtaglomerular apparatus which maintains perfusion by autoregulation of arterial pressure; and

2. a juxtamedullary group subjected to a passive increase in flow as arterial pressure rises.

A redistribution of blood flow to the juxtamedullary group in response to a falling cardiac output could account for the salt retention of heart failure (Hamer, 1982 - p.7).

5. Other Humoral Agents:

Anti-diuretic hormone contributes to water retention in heart failure by effecting distal renal tubular function (see section 1.6). Other vasoactive substances such as prostaglandins, kallikreins and kinins have also been implicated as important factors in sodium balance (McGiff & Itslovitz, 1973; Mills et al, 1976), but their precise role in heart failure is, as yet, unclear and requires further research and the development of sensitive assays for these hormones.

1.4 THE ROLE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN HEART FAILURE :

1. Physiology:

Aldosterone, the most potent mineralocorticoid secreted by the adrenal cortex, plays a major role in sodium and potassium homeostasis. Enhanced distal tubular sodium-potassium exchange by aldosterone promotes sodium retention and potassium depletion. Four regulators of aldosterone release are well defined:

1. the renin-angiotensin system;
2. plasma potassium;
3. ACTH;
4. plasma sodium.

Of these, the first two are generally considered to be the most important (Hollenberg & Williams, 1981). Other regulators have been suggested, including dopamine, which is thought to have a tonic inhibitory effect on aldosterone secretion (Campbell et al, 1981). Normally, more than 75% of the circulating aldosterone is inactivated during a single passage through the liver. However, in the presence of heart failure, this percentage may be reduced (Tait et al, 1965; Camargo et al, 1965). In an otherwise normal subject, and in primary aldosteronism, excess levels of aldosterone per se do not usually lead to oedema formation because of the so-called "escape phenomenon". To prevent this from occurring proximal sodium reabsorption decreases, but the precise "escape" mechanism remains to be explained (Urqhart & Davis, 1963; Johnson et al, 1968). In heart failure, however, proximal tubular sodium reabsorption is enhanced, and the "escape" from aldosterone effect does not occur, thus this hormone contributes to the increase in extracellular volume.

Renin is a proteolytic enzyme produced and stored in the granules of the juxtaglomerular cells. Released renin splits the deca-peptide angiotensin I from its circulating substrate,

the alpha-2 globulin called angiotensinogen. Circulating renin has a plasma half-life of 10-15 minutes (Levens, Peach & Carey 1981). In the presence of angiotensin converting enzyme (found in all tissues, but predominently pulmonary endothelium), angiotensin I is converted into the biologically active octapeptide, angiotensin II. This hormone is a potent direct stimulus both to aldosterone and constriction of vascular smooth muscle, while it is destroyed rapidly by angiotensinases, thus it has a half-life in the order of minutes. Renin release is controlled by a composite of four interdependent factors (Oparil & Haber, 1974):

1. Thè juxtaglomerular cells act as miniature pressure transducers that sense changes in afferent arteriolar perfusion pressure. When the circulating blood volume is reduced, a corresponding fall in afferent arteriolar pressure and renal perfusion pressure occurs. Renin is then released by these cells to restore blood volume to normal through the effect of angiotensin II on aldosterone, and perhaps directly on the kidney (Levens et al, 1981).

2. The Macula Densa cells are thought to function as chemoreceptors, monitoring the sodium or chloride load present in the distal tubule, and feeding this information back to the juxtaglomerular cells, where appropriate modifications in renin release occur.

3. The sympathetic nervous system plays a prominent role in regulating renin secretion mediated by beta-receptors.

4. A number of circulating factors may alter renin release. These include ADH, angiotensin II, and potassium (Abbrecht & Vander, 1970).

2. Activity of the Renin-Angiotensin-Aldosterone System in Heart Failure:

Elevation of plasma renin activity and aldosterone concentration in subjects with heart failure has not been consistently observed (Merrill et al 1946, Brown et al 1970, Sanders and Melby 1964, Wolff et al 1959, Genest et al 1968, Chonko et al 1977). Recent experimental studies in conscious animals with cardiac failure have suggested that the renin-angiotensin-aldosterone system is activated soon after the induction of a low cardiac output (Watkins et al, 1976; Freeman et al, 1979; Morris et al, 1977; Davis 1962). During the chronic compensated state of experimental heart failure, plasma renin activity and plasma aldosterone concentration decrease toward normal as the extracellular fluid volume expands (Watkins et al, 1976; Davis, 1962). Thus, the discrepancies in the state of the renin-angiotensin-aldosterone system in the clinical literature are probably due to lack of clear definition of the clinical status of the patients studied, and failure to control other factors affecting both renin and aldosterone secretion.

Dzau et al (1981) found that during acute, severe left ventricular decompensation, before the development of extracellular fluid volume expansion and restoration of systemic blood pressure, plasma renin activity and aldosterone were markedly elevated. With stabilisation of cardiac failure and extracellular fluid expansion, plasma renin activity and aldosterone returned to apparently normal levels although they remained abnormally elevated for the degree of blood volume expansion.

In patients with severe heart failure, Nicholls et al (1974) demonstrated a biphasic response of resting plasma renin activity and aldosterone to frusemide induced diuresis. Prior to treatment, a modest increase in these hormones was evident. During the diuretic phase there was a paradoxical suppression of

the renin-angiotensin-aldosterone system, presumably as a result of increased distal tubular sodium load (Vander, 1967). As the patients approached dry body weight with continued diuretic therapy, plasma aldosterone concentrations rose to very high levels (Nicholls et al 1974; Knight et al, 1979). The parallel rise in plasma renin activity (Nicholls et al, 1974) suggested that the renin-angiotensin system (rather than other known secretagogues) controlled this pattern of aldosterone change. Sodium load to the distal tubule will be low at this stage, as there is little further diuresis, and continued intense diuretic therapy can maintain dry body weight, while augmenting renin release.

The potentiating effect of diuretic therapy on the activity of the renin-angiotensin-aldosterone system in heart failure, may increase ventricular afterload and could hasten the progression of heart failure (Maslowski et al, 1981a). These points are considered in greater detail in Chapter 8, where I discuss the stability of hormone, haemodynamic and electrolyte observations and their inter-relationships in twenty-one patients with heart failure on constant digoxin and diuretic therapy.

3. Pharmacological Interruption of Renin-Angiotensin Activity:

The development of agents that block the renin-angiotensin system has provided pharmacological probes that are useful in assessing more directly angiotensin's contribution to heart failure. Blockade may be effected at three levels:

1. Beta-adrenergic antagonists suppress renin release, but this class of drug has contributed little to our understanding of renin's role in heart failure because of confounding effects on myocardial function in heart failure (Hollenberg & Williams 1981);

2. Angiotensin converting enzyme inhibitors (eg. teprotide, captopril, and more recently, enalapril) which block the formation of angiotensin II;

3. Angiotensin II analogues (eg. saralasin) which compete directly with angiotensin II at its receptor site. These antagonists appear to be more specific in their action than converting enzyme inhibitors, however they can only be given intravenously, are expensive to synthesise, and like most receptor antagonists, they have some agonist action.

It should be noted that there is much debate concerning the specificity of the action of converting enzyme inhibitors. This enzyme is responsible, in part, for degradation of bradykinin, a powerful vasodilator, but levels do not appear to be elevated by captopril (Johnston et al 1979, Dzau et al 1980). Clarification of bradykinin's role in heart failure, and the effects of converting enzyme inhibitors await the development of assays which are more sensitive than those currently in use. Captopril may affect prostaglandins which also modulate vascular tone, but available evidence is divergent (Romankewicz et al, 1983).

4. Renin-Angiotensin Blockade in Heart Failure:

Agents that interrupt the renin-angiotensin axis activity have shown promise in animal models (Watkins et al 1976, Freeman et al 1979) and clinical studies (Dzau et al 1980, Faxon et al 1980, Maslowski et al 1981a, Turini et al 1979). Acute pharmacological blockade of the renin-angiotensin system with converting enzyme inhibitors or angiotensin analogues has produced salutary response in a large majority of patients with severe heart failure. Haemodynamic improvement resembles the response seen with nonspecific vasodilators (eg. nitroprusside - Vrobel et al, 1980). Since both classes of agents have been effective, it is very likely that a substantial portion of the vascular response in heart failure reflects reversal of the vasoconstriction induced by angiotensin (Hollenberg & Williams, 1981).

Captopril, the only currently available oral converting enzyme inhibitor, has been studied in patients resistant to conventional therapy. Although side effects are not common, potentially serious complications have been reported (Vidt, Bravo & Fouad, 1982). Enalapril, a member of a new group of converting enzyme inhibitors which lacks a mercapto function and is characterised by weak chelating properties, has recently been synthesised (Patchett et al, 1980) and used successfully in hypertension (Gavras et al, 1981). Preliminary data suggest it is as effective and longer acting than captopril in hypertension (Gavras et al, 1981), and so far serious side effects have not been observed, paving the way for its use in patients with milder degrees of cardiac failure. To date the haemodynamic, hormonal and electrolyte response to enalapril in heart failure have not been documented. In chapter 6, I report the results of such a study in nine patients with heart failure stable on digoxin and diuretic therapy.

In an earlier report from this unit (Maslowski et al, 1981b), the effects of withdrawal of long term captopril therapy

were observed for four days in five patients. Acute haemodynamic rebound was not seen, which may be taken to suggest that the drug has little or no effect in the long-term, or alternatively, that four days is insufficient time for the return of cardiac failure. In chapter 10, I report the results of a one month double-blind trial investigating withdrawal of captopril. These are the only investigations that have addressed the long-term effectiveness of converting enzyme inhibitors in such a manner.

1.5 THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM :

In view of the well established importance of the sympathetic nervous system in normal regulation of the circulation, considerable attention has been directed to the activity of this system in heart failure. In 1962, Chidsey et al noted that either no change or very small increases in plasma norepinephrine occurred in normal subjects with exercise, while much greater rises occurred in patients with heart failure, presumably reflecting greater activity of the sympathetic nervous system during exercise. Measurements of 24 hour urinary norepinephrine excretion revealed marked elevations in patients with heart failure, suggesting greater activity at rest as well (Chidsey, Braunwald & Morrow; 1965).

Plasma catecholamines provide a view of "global" sympathetic activity (Goldstein, 1981), but they do not provide information on regional tone. A further limitation is that plasma norepinephrine reflects both "spillover" rate from sympathetic nerve endings and clearance rate from plasma (Esler et al, 1981). Hence, some caution must be exercised in equating plasma norepinephrine with sympathetic tone.

The sympathetic nervous system plays little part in determining normal myocardial function in the basal state (Braunwald, 1979). In the presence of myocardial failure, however, reliance on enhanced sympathetic activity is indicated by intensification of heart failure after sympathetic blockade with guanethidine (Gaffney & Braunwald, 1963) or propranolol (Epstein & Braunwald, 1966). More recently some doubt has been cast on the supportive role of the sympathetic nervous system in dilated cardiomyopathy (Waagstein et al, 1975; Swedberg et al, 1979, 1980a, 1980b). These researchers report paradoxical therapeutic benefit from beta-blockade in patients afflicted by this disorder, but these findings have not been confirmed by other workers as yet.

The investigation described in Chapter 9 provides the first double-blind controlled study of the effect of beta-blockade in dilated cardiomyopathy. The results from this study do not support the Swedish viewpoint, and in that chapter I look critically at the Swedish data.

Depletion of myocardial norepinephrine stores (Chidsey et al 1965,1966) provides further evidence for abnormal adrenergic activity in heart failure. As a result, the heart fails to respond to sympathetic input with increasing heart failure. Goldstein et al (1975) demonstrated an impaired chronotropic response to atropine and baroreceptor-mediated reflexes which appears to be related to severity of heart disease. They observed a normal response to isoprenaline indicating the abnormality in sympathetic response results from presynaptic norepinephrine depletion, rather than a reduction in responsiveness of beta-receptors. In pre-terminal patients undergoing cardiac transplantation, however, depletion of beta-receptors and diminished responsiveness to catecholamines in vitro has recently been reported (Bristow et al, 1982).

Substantial changes also occur in the function of the adrenergic nerves which innervate peripheral blood vessels in heart failure. Thus, while adrenergically mediated vasoconstriction normally occurs in the vessels supplying the splanchnic viscera and kidneys during exercise (Braunwald et al, 1976), neurogenic vasoconstriction is even more important when cardiac output is seriously limited, as in heart failure. Increased adrenergically mediated vasoconstriction in the limbs occurs at rest only in the presence of severe heart failure (Higgins et al, 1972), however even in milder forms of heart failure a marked sympatho-adrenal discharge occurs during exercise. In the presence of a limited cardiac output, this discharge apparently acts to maintain arterial pressure and aids in the perfusion of essential organs, such as the brain and heart, at the expense of the exercising, metabolically active muscles (Higgins et al, 1972).

This peripheral vasoconstriction is mediated by alpha-adrenergic receptors (Kramer et al, 1968). In patients with heart failure, blockade of these receptors with agents such as prazosin reduces ventricular afterload, and acute haemodynamic improvement associated with symptomatic improvement has been reported (Miller et al, 1977; Mehla et al, 1978). At least two centres have presented objective haemodynamic data to suggest that tolerance to prazosin occurs and develops rapidly (Packer et al, 1978; Arnold et al, 1978). Furthermore, Colucci et al (1980b) noted an increase in plasma renin activity, with many patients requiring an increase in diuretic dosage. Thus activation of the renin-angiotensin system may be involved in the development of tolerance to long-term prazosin therapy.

In the later stages of heart failure, when the levels of circulating catecholamines are elevated and the cardiac norepinephrine stores depleted, the myocardium depends to a large extent on greater adrenergic stimulation. Some writers have speculated that the heart derives much of this stimulation from circulating catecholamines, (Braunwald, 1979), but circulating norepinephrine is not active on heart, vessels, or metabolism until it reaches plasma levels of about 2,000 pg/ml (Silverberg et al, 1978). Elevated sympathetic activity peripherally, however, increases vascular resistance and may present the heart with an excessive afterload. Recently, several selective beta-receptor agonists have become available (Dawson et al, 1981; Waagstein et al, 1979) which may provide inotropic support, without adversely affecting ventricular afterload. The haemodynamic, hormonal and electrolyte effects of acute administration of one of these new agents, prenalterol, are presented in Chapter 7.

1.6 ROLE OF ANTIDIURETIC HORMONE IN HEART FAILURE :

1. Physiology:

Antidiuretic hormone (ADH or arginine -vasopressin) is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus. Packaged in neurosecretory granules by the endoplasmic reticulum, ADH is then transported along the axons to their bulbs in the posterior pituitary where it may be released into the circulation by exocytosis (Schrier & Leaf, 1981). The role of ADH in water homeostasis has received most attention but it does have vasoconstrictor properties which may be of physiological and pathophysiological importance (Johnston et al, 1981).

Release of ADH is controlled by osmotic and non-osmotic pathways (Schrier, Berl & Anderson, 1979):

1. "Osmoreceptor cells" which apparently lie outside the blood-brain barrier sense changes in extracellular osmolality induced by fluid deprivation or ingestion and increase or decrease ADH release respectively. ADH enhances distal tubular water reabsorption, thus water deprivation decreases free water clearance, while water excess increases its clearance.

2. The major non-osmotic stimuli for ADH release include depletion of the extra-cellular fluid and hypotension, however pain, fright, nausea, and hypoxia may also stimulate release (Robertson et al, 1977; Schrier et al, 1979). Major parasympathetic afferent pathways appear to arise from low-pressure atrial receptors (vagal), which perceive early changes in the volume of the extra-cellular fluid, and from high-pressure baroreceptors of the carotid sinus (glossopharyngeal nerve) and aortic arch (vagal) which probably perceive more severe derangements in volume and pressure.

2. ADH Activity in Heart Failure:

Hyponatraemia occurs frequently in patients with heart failure who have a moderate water intake (Bartter, 1964). At present it is not clear whether persistent release of ADH which diminishes water clearance, or intrarenal factors account for this hyponatraemia. The vasoconstrictor role of ADH in heart failure has received scant attention. A specific inhibitor of the vasoactive action of ADH is now available (Seto et al, 1980), but it has not yet been used to investigate the role of ADH induced direct vasoconstriction in heart failure.

Early studies using bioassay to measure plasma ADH in patients with heart failure have not been definitive (Sztalowicz et al, 1981). Using a radioimmunoassay for ADH, these authors recently demonstrated higher ADH levels in heart failure patients when hyponatraemia and hypo-osmolarity were more severe. This supports the role of ADH in impaired water excretion in heart failure and implies that nonosmotic pathways, rather than osmotic pathways, provide the main stimulus for ADH release under these circumstances, confirming findings from animal studies (Anderson et al 1975,1976; Handelman et al, 1979). What factor(s) dictate this "inappropriate" elevation in ADH levels is not clear, but possibilities include impaired inhibition of ADH release in response to atrial stretch or volume receptors (Greenberg et al, 1973) or parasympathetic stimulation from high pressure baroreceptors when "effective" blood volume is reduced (Schrier & Humphries, 1971).

To date, plasma levels of ADH measured by radioimmunoassay have not been related to haemodynamic parameters and other hormonal levels. Such measurements were performed in thirteen patients with stable heart failure and results are presented in Chapter 8. The effect of diuretic therapy on ADH levels is also discussed, while the effect of converting enzyme inhibition is discussed in Chapter 6.

1.7 POSSIBLE ROLE OF PERIPHERAL VASOCONSTRICTION IN THE NATURAL HISTORY OF HEART FAILURE :

The syndrome of heart failure is a naturally progressive disorder that often appears to worsen without any evidence for an active process within the myocardium (Cohn et al, 1981). Studies of cardiac mechanics have suggested that progression of heart failure may represent an inappropriate increase in wall tension associated with an enlarging chamber without concomitant increase in wall thickness (Strauer, 1979). Peripheral vasoconstriction may well be an important mechanism in the genesis of this cardiac dilatation (Cohn et al, 1981). Constriction of small arteries and reduced distensibility of large arteries increases impedance to left ventricular ejection and increases left ventricular end-systolic volume.

Chronic heart failure can be looked upon as a vicious cycle initiated by a cardiac lesion that impairs cardiac performance and results in reduced cardiac output (see fig 6.2). This low output may initially be compensated by activation of neurohumoral systems, which eventually elevate systemic vascular resistance, in turn increasing resistance to ventricular outflow. For the failing ventricle, this further depresses ventricular performance, thereby completing a positive feedback loop.

Conventional treatment often fails to significantly increase cardiac output or lower systemic resistance, thus the cycle outlined above remains intact. Diuretic therapy may accelerate the cycle by activating the renin-angiotensin system (see chapter 8). Blockade of the vasoconstrictor systems may well reverse this situation, thereby improving prognosis (Franciosa et al, 1981). Much research will be required to demonstrate this and also to find the best agent(s) to obtain this goal.

1.8 OBJECTIVES OF THIS THESIS :

To summarise, heart failure is associated with a poor prognosis, and it is one of the most common causes of death in our society. Despite advances in other fields of cardiology, research has produced little impact on the morbidity and mortality of this serious syndrome. Evidence has been produced to show that neurohumoral systems are integrally involved in the pathophysiology and possibly with the progression of heart failure. Better therapy is likely to follow improved knowledge of the role of these systems in heart failure.

In the studies incorporated in this thesis, I explore some facets of this large, and fascinating field of research. The acute haemodynamic, hormone and electrolye effects of blockade of the renin-angiotensin-aldosterone system and beta-1 adrenergic stimulation are discussed in Chapters 6 & 7 respectively. The current role of vasodilator and inotropic therapy in heart failure will be outlined at the beginning of each chapter. From these studies, control data is utilised to document stability of haemodynamic, hormone and electrolyte measurements and their inter-relationships in heart failure (Chapter 8). In Chapter 9, I investigate the long-term effects of blocking the beta receptor of the sympathetic nervous system in dilated cardiomyopathy. Finally, in Chapter 10, I discuss the effect of withdrawal of blockade of the renin-angiotensin-aldosterone system. These studies contribute significantly to our growing fund of knowledge concerning the role of neurohumoral systems and applications of this knowledge in medical therapy are considered.

Before describing these studies in detail, methods of patient selection will be outlined in the next chapter, then methods used in the above studies for non-invasive, haemodynamic, and hormone measurements are detailed in the subsequent three chapters.

CHAPTER 2

PATIENT SELECTION:

2.1 INTRODUCTION :

Over the past decade the Cardiology and Endocrinology Departments of The Princess Margaret Hospital, Christchurch have had an ongoing interest in the investigation of the pathophysiology and management of heart failure. Consequently, a good rapport has been established between these departments and general practitioners and physicians in the region so that most patients developing heart failure are referred for diagnosis and management of their condition. The Cardiology Department serves the province of Canterbury, thus it services a population of approximately 400,000 people.

With diverse aetiology, manifestations and multiple exacerbating factors, heart failure is a heterogeneous syndrome. In the studies to be described in this thesis, I attempted to select a relatively homogeneous group of patients. Patients were only selected if heart failure was due to left ventricular dysfunction. Definition of heart failure, aetiology, inclusion, and exclusion criteria are outlined in this chapter. Ethical considerations are then discussed.

2.2 DEFINITION OF HEART FAILURE:

"Heart failure may be defined as the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues."

Braunwald (1982)

Heart failure is an imprecise term which is usually defined (as above) as a state in which the heart is unable to generate a cardiac output equal to the body's demands. Clinical manifestations are largely due to circulatory failure (fatigue, diminished exercise capacity, dyspnoea, and oedema), manifestations which may occur in other conditions other than primary cardiac disease (eg. hypovolaemia, anaemia, hyperviscosity, hyperthyroidism and pulmonary embolism). Left ventricular dysfunction was confirmed in all cases by non-invasive or invasive investigations (see Chapter 3), while other conditions were excluded by specific investigations.

2.3 AETIOLOGY OF HEART FAILURE:

Abnormal cardiac function resulting in circulatory failure may be due to:

1. Pressure overload: eg. aortic or pulmonary stenosis or hypertension.

2. Volume overload: eg. valvular incompetence or shunts.

3. Impaired myocardial function: eg. myocardial ischaemia/infarction, scarring, infiltrative disorders, toxic insults, primary and secondary cardiomyopathy.

4. Extrinsic compression of the heart: eg. pericardial constriction or effusion.

Prior to enrolment in the following studies, all patients underwent exhaustive diagnostic studies, including cardiac catheterisation and coronary angiography in most patients. Thus, precise anatomical diagnosis was established. Impaired myocardial function was largely due to coronary artery disease or primary dilated cardiomyopathy, although hypertension contributed in some patients. When any condition in the first two categories is allowed to persist for long periods of time, secondary changes may develop in the myocardium that then contribute to reduced pump performance and hence to heart failure. Several patients were included with valvular incompetence, only when myocardial function was severely depressed.

2.4 INCLUSION CRITERIA WERE AS FOLLOWS:

1. Presence of symptoms directly attributable to left ventricular failure;

2. Absence of a surgically correctable lesion eg. coronary artery disease or valvular lesion;

3. Clinical, radiographic, and/or haemodynamic evidence of left ventricular failure;

4. Absence of exacerbating factors eg. infection, anaemia, thyrotoxicosis, pregnancy, arrhythmias other than atrial fibrillation, recent myocardial infarction (< six months), infection or malignant hypertension.

2.5 EXCLUSION CRITERIA INCLUDED:

1. Absence of symptoms attributable to myocardial failure;

2. Unstable clinical condition;

3. Presence of exacerbating factors;

4. Unstable angina or myocardial infarction within the previous six months;

5. Diabetes mellitus was an exclusion criteria in some studies because hormone responses, especially catecholamines, may be abnormal;

6. Severe concomitant illness;

7. Severe peripheral vascular disease where claudication limited exercise tolerance much more than cardiac symptoms.

2.6 ETHICAL CONSIDERATIONS:

The guidelines of the Helsinki Convention for human experimentation were followed implicitly (18th World Medical Assembly, Helsinki, 1964 and subsequently revised by the 29th World Medical Assembly, Tokyo, 1975). For each investigation included in this thesis, the protocol was perused by the physicians involved, then submitted to and approved by the Ethical Committee of the North Canterbury Hospital Board. Patients were fully informed of the techniques used in each study, possible dangers and were free to withdraw from the investigation at any time. All patients gave written consent.

In any study involving instrumentation of patients, however limited, the question of ethical justification arises. Most patients included in the studies documented in this thesis had severe heart failure, having had at least one documented episode of pulmonary oedema and also documented severe impairment of left ventricular function. Invasive measurement is an important method for assessing the efficacy of therapy in heart failure (Braunwald, 1980b). It can be performed safely, so long as adequate precautions are taken. The low incidence of complications in the following studies would confirm this.

CHAPTER 3

ASSESSMENT OF THE SEVERITY OF HEART FAILURE AND RESPONSE TO THERAPY:

3.1 INTRODUCTION:

Over the last decade we have seen a rapid increase in the number of methods available for cardiac diagnosis. Aetiology may now be determined with greater accuracy, and prognosis may be forecast with greater certainty. The quantitative assessment of the severity of heart failure and underlying myocardial dysfunction remains a problem in clinical cardiology as no single method provides a "gold standard" to compare patients or their response to therapy. This is a challenging and important task for clinicians, thus a plethora of methods have been devised to suit different purposes:

1. Clinical Assessment: Symptoms and physical findings.

2. Invasive Methods:

    1. Haemodynamics - Pressure, flow relationships;
    2. Left ventricular force-velocity-length relationships;
    3. Quantitative Angiocardiography.

3. Non-invasive Methods:

    1. Radionuclide Angiography;
    2. Echocardiography;
    3. Systolic Time intervals;
    4. Apex and phonocardiography;
    5. Assessment of heart size by chest radiography.

4. Exercise Testing: Exercise may be accurately assessed on a treadmill or bicycle ergometer. Useful adjuncts to this assessment include invasive haemodynamics measured during exercise and quantification of oxygen uptake, carbon dioxide production and anaerobic threshold.

Quantitative angiocardiography and left ventricular force-velocity-length relationships require left ventricular catheterisation. Due to the risk of embolisation studies can only be performed over a short period of time, and were not suitable for the present studies. Systolic time intervals and phonocardiography are too imprecise for adequate assessment (Braunwald, 1980).

Methods for assessing cardiac function used in this thesis will be detailed in this chapter. Haemodynamic measurements will be considered in greater detail in the next chapter.

3.2 CLINICAL ASSESSMENT:

As muscular exercise places the greatest metabolic stress on the heart, it is hardly surprising that the severity of heart failure may be assessed clinically by paying attention to exertional symptoms particularly dyspnoea and fatigue. The New York Heart Association (NYHA) Classification (1973) has been the most widely accepted, and has been used throughout this thesis. Patients were classified as follows:

1. Class I: No limitation - ordinary physical activity does not cause undue fatigue or dyspnoea.

2. Class II: Slight limitation of physical activity - such patients are comfortable at rest. Ordinary physical activity results in fatigue or dyspnoea.

3. Class III: Marked limitation of physical activity - although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

4. Class IV: Inability to carry on any physical activity without discomfort - symptoms of congestive failure are present even at rest. With any physical activity, increased discomfort is experienced.

Physical signs of heart failure only become apparent when myocardial dysfunction is severe and due to their subjective nature, measurement is difficult, thus more precise methods are required to quantitatively assess the effect of medications, especially in patients who are less severely afflicted.

3.3 HAEMODYNAMIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION:

Direct measurement of haemodynamic parameters, cardiac output and vascular pressures, has become the time honoured method for assessing the severity of cardiac function and the effects of therapeutic intervention (Braunwald, 1980). To aid the interpretation of the haemodynamic studies reported in this thesis, it is useful to review circulatory dynamics at rest and during exercise in normal and pathological circumstances according to the Frank-Starling mechanism:

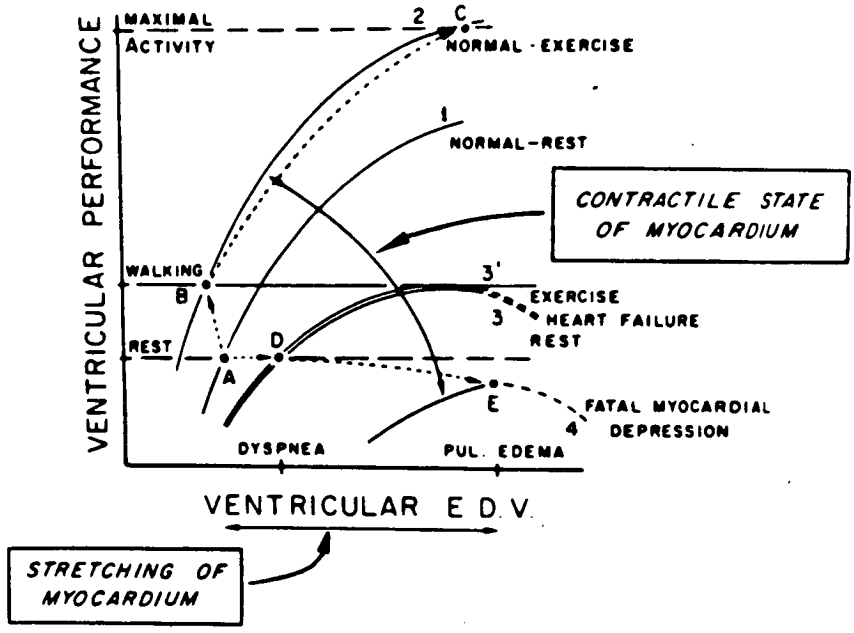
1. Normal Myocardial Function:

The normal relationship between ventricular end-diastolic volume and performance is shown in Fig 3.1, curve 1. Assumption of the upright posture reduces venous return, thus cardiac output is lower than in the recumbent position. During exercise, venous return is augmented by increased ventilation, the pumping action of exercising muscles and venoconstriction. Increased sympathetic activity simultaneously augments the contractile state of the myocardium and stroke volume, with either no change or a decline in end-diastolic pressure and volume (resulting in a shift from point A on curve 1 to point B on curve 2 in fig 3.1). Vasodilatation occurs in the exercising muscles, thus cardiac output is greatly elevated during exercise at an arterial pressure only slightly higher than that in the resting state. During intense exercise, cardiac output may be further augmented by utilisation of the Frank-Starling mechanism (B - C, fig 3.1).

2. Impaired Myocardial Function:

In many cases, such as those represented in curve 3 (fig 3.1), cardiac output and external ventricular performance at rest are often within normal limits, but are maintained at these levels only because the end-diastolic fibre length and ventricular end-diastolic volume are elevated. Associated elevation of the pulmonary capillary wedge pressure and venous congestion contribute to the dyspnoea experienced by patients with heart failure on exertion (D).

FIGURE 3.1:



This diagram shows the inter-relationships of diastolic stretching of the myocardium and contractility on vetricular performance. (From Braunwald et al, 1976 - see text for detailed description).

Ventricular performance curves or contractility cannot be elevated to the same extent during exercise (compare curves 3 & 3', fig 3.1) because cardiac epinephrine stores are depleted and the inotropic response to impulses from the cardiac sympathetic nerves is diminished (see Chapter 1). Factors that tend to augment ventricular filling during exercise in the normal subject, push the failing heart along its flattened length to active tension curve. Although ventricular performance may be augmented somewhat, this occurs only as a consequence of an inordinate elevation of ventricular end-diastolic volume and pressure, and therefore of pulmonary capillary wedge pressure. This intensifies dyspnoea and plays an important role in limiting the level of exercise that the patient can perform.

Left ventricular failure is thus characterised haemodynamically by elevated left ventricular filling pressure and reduced cardiac output (especially during exercise), which account for the pulmonary congestion and peripheral underperfusion. Heart rate is increased in an effort to maintain cardiac output, while systemic arterial pressure is usually supported at normal levels, despite reduced cardiac output, consequently systemic vascular resistance is usually elevated. Quantitative measurement of these parameters allows accurate assessment of the degree of myocardial dysfunction (Braunwald, 1980). Furthermore, invasive measurement of haemodynamic changes provides a useful tool for assessing the efficacy of therapeutic agents (Liander, 1982). Therapeutically induced reduction in left ventricular filling pressure and increase in cardiac output, is beneficial according to Frank-Starling function curves, and has been associated with acute symptomatic benefit and long-term efficacy (Braunwald, 1980).

As with all methods of assessing cardiac function, there are limitations which need to be appreciated:

1. Measurement of left ventricular performance at rest does not necessarily provide an accurate assessment of cardiac reserve and ability to perform exercise (Franciosa et al, 1979);

2. Left ventricular filling pressure is used as an approximation for left ventricular end-diastolic volume which determines stretch of myocardial fibres. This is a valid extrapolation in the presence of normal compliance, however in disease states compliance is often abnormal (Liander, 1982);

3. In disease and health, cardiac output is closely controlled by auto-regulation (Guyton, 1981), thus resting cardiac output is only depressed when ventricular dysfunction is severe;

4. Some studies have demonstrated improved exercise capacity during long-term therapeutic interventions that were not associated with significant haemodynamic changes at rest (Franciosa et al 1978, Rubin et al 1979).

Despite these limitations, haemodynamic measurements remain the best method currently available for quantitatively assessing the degree of myocardial dysfunction and response to therapy, especially when serial measurements over several days are required. Methods for measurement of cardiac output, and intra-cardiac pressures will be outlined in detail in the next chapter.

3.4 RADIONUCLIDE ANGIOGRAPHY:

1. General:

Since Blumgart and Yens (1927) first used a radioactive tracer to evaluate the velocity of blood flow in man, substantial improvements have been made in imaging devices, isotopes and computer techniques. Consequently, these techniques have been applied to radionuclide angiographic assessment of cardiac function, and particularly to left ventricular function, for which ejection fraction (LVEF) has become the most widely used parameter.

Studies were initially performed with a gamma-camera located at the Nuclear Medicine Department of The Christchurch Hospital four miles from the Cardiology Department situated at The Princess Margaret Hospital. This necessitated the transfer of patients for cardiac scans. To obviate this, a "Nuclear Stethoscope" (Bios Instruments) was purchased by the department and isotopes were delivered to the Department in a lead cannister prior to use.

2. Blood Labelling:

The need to perform counts for several minutes requires that the isotope remains within the circulation. In the present studies, in-vivo labelling of red blood cells (Pavel, Zimmer and Patterson, 1977) was achieved by intravenous administration of 7 mg of stannous pyrophosphate thirty minutes before intravenous injection of 15-20 mCi of technetium-99m sodium pertechnetate. This provided sufficient "tag" for studies to be performed for several hours after administration of the isotope if required.

3. Principle of calculations:

A count based technique, utilising computer-derived plots for changes in counts from end-diastole to end-systole against time, was used to calculate left ventricular ejection fraction. The major limitation of this technique involves appropriate correction for

background activity arising from the lung fields, left atrium, and right heart. In all studies, a small zone just lateral to the left ventricle was used.

Ejection fraction was calculated by the equation:

$$LVEF = \frac{\text{End-diastolic - End-systolic counts}}{\text{End-diastolic - Background counts}} \times 100$$

4. Gamma-camera studies:

Resting studies were performed with the patient supine and images obtained in the modified (caudal tilt) left anterior oblique position using a Picker Dyna camera equipped with a high-resolution parallel-hole collimator. Scintillation data was accumulated in histogram mode (64 x 64 ward mode images) in a PDP 11-34 computer system using the R Wave of the ECG as the synchronising impulse. The cardiac cycle was divided into twelve equal frames, and three hundred cycles were counted.

Calculation of LVEF was performed using a commercially available modified Fortran Decus HRTIMG program (Decus No. 11-363, August 1978). This program uses an automatic stepping, automatic edge finder routine after selection of an end-diastolic region of interest. Background was calculated from a simple level subtraction and was chosen from the end-systolic frame as a two pixel postero-lateral 90^{o} crescent immediately adjacent to the end-systolic left ventricular border. A background corrected time activity curve was displayed and LVEF calculated from the formula given above.

Validation studies from the Nuclear Medicine Department have shown:

1. A good correlation between LVEF derived from contrast angiography and radionuclide technique ($r=0.84$; $n=23$; $p<0.0001$).

2. Studies in normals (n=10) showed mean resting EF=62% (range 50-73%).

3. Mean serial variability of absolute ejection fraction in repeated studies on two different days: 6 ± 4.3% (9 normal patients) and 3 ± 2.4% (10 patients with coronary artery disease).

5. Nuclear Stethoscope:

The "Nuclear Stethoscope" consists of a single scintillation probe with a 2 by 1.5 inch sodium iodide crystal and a slightly conical collimator with an outer opening of 3 cm diameter. The probe is carried by an adjustable arm allowing angulation in two different planes. Radioactivity is sampled and displayed with a temporal resolution of 10 msec (ventricular function mode) or 50 msec (beat-to-beat mode) per datum point. A dedicated microcomputer calculates left ventricular ejection fraction and other parameters. Together with the time-activity curve these data are displayed on a screen and could be reproduced by a Tecktronix Recorder.

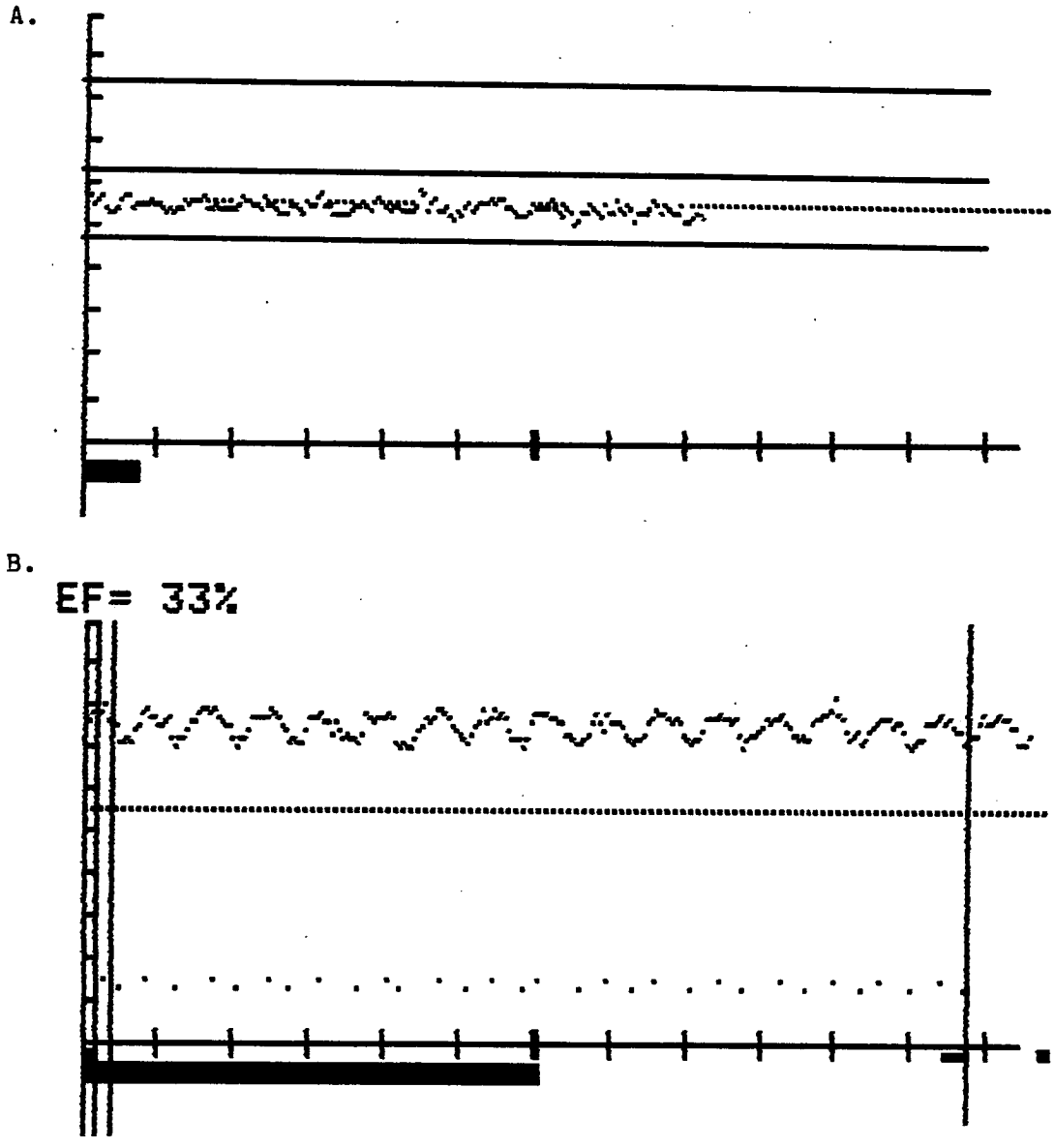
With the probe positioned over the chest in a 35° left anterior oblique position with 5° caudal tilt, the precordium was scanned in parallel movements from right to left and in the cranio-caudal direction to approximate the left ventricular position. Small adjustments of the initial probe angulations were made if required according to individual chamber localisations. Correct positioning was guided by a search for maximal extension of a broad horizontal bar (fig 3.2B). The length of this bar is proportional to the amplitude of the time-activity curve and inversely proportional to the mean count rate.

Background activity was recorded at a position inferolateral to the heart, where the mean count rate is relatively low and the amplitude of the time-activity curve minimal, but still detectable, rendering also the bar length minimal (fig 3.2A). This background activity was coded into the computer and used for all calculations

of left ventricular ejection fraction. The probe was subsequently moved back to the left ventricular position for recording of the gated time-activity curve (for two R-R intervals - Ventricular Function Curve). Left ventricular ejection fraction was calculated by moving two vertical cursors to positions corresponding to the end-diastolic and end-systolic count rate of the displayed mean time-activity (fig 3.3).

All investigations using the Nuclear Stethoscope were performed by the author. To validate the technique, left ventricular ejection fraction was determined by Gamma Camera and Nuclear Stethoscope in ten patients with ischaemic heart disease. Results of this study show good correlation between the two methods ($r=0.85$, $p<0.001$) as shown in fig 3.4. These results are similar to the findings of Hoilund-Carson et al (1982). In another validation study, ejection fraction was determined on two occasions two weeks apart in another group of ten patients with heart failure stable on constant medication. Overall, mean ejection fraction was the same ($22.5 \pm 13.4\%$) on both occasions while mean variability of absolute ejection fraction on the two days was $4.1 \pm 1.6\%$ comparing well with gamma camera studies.

FIG 3.2

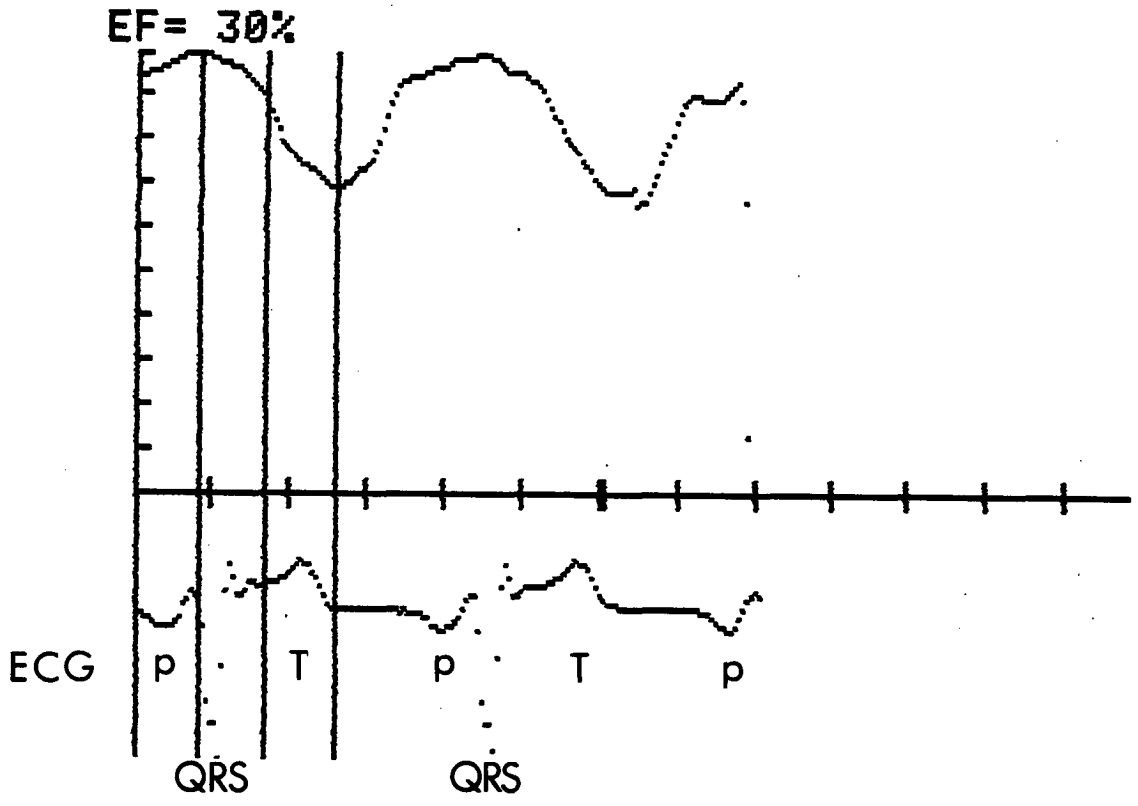


Determination of ejection fraction by "Nuclear Stethoscope":

A. Determination of background counts (note minimum excursion of horizontal bar)

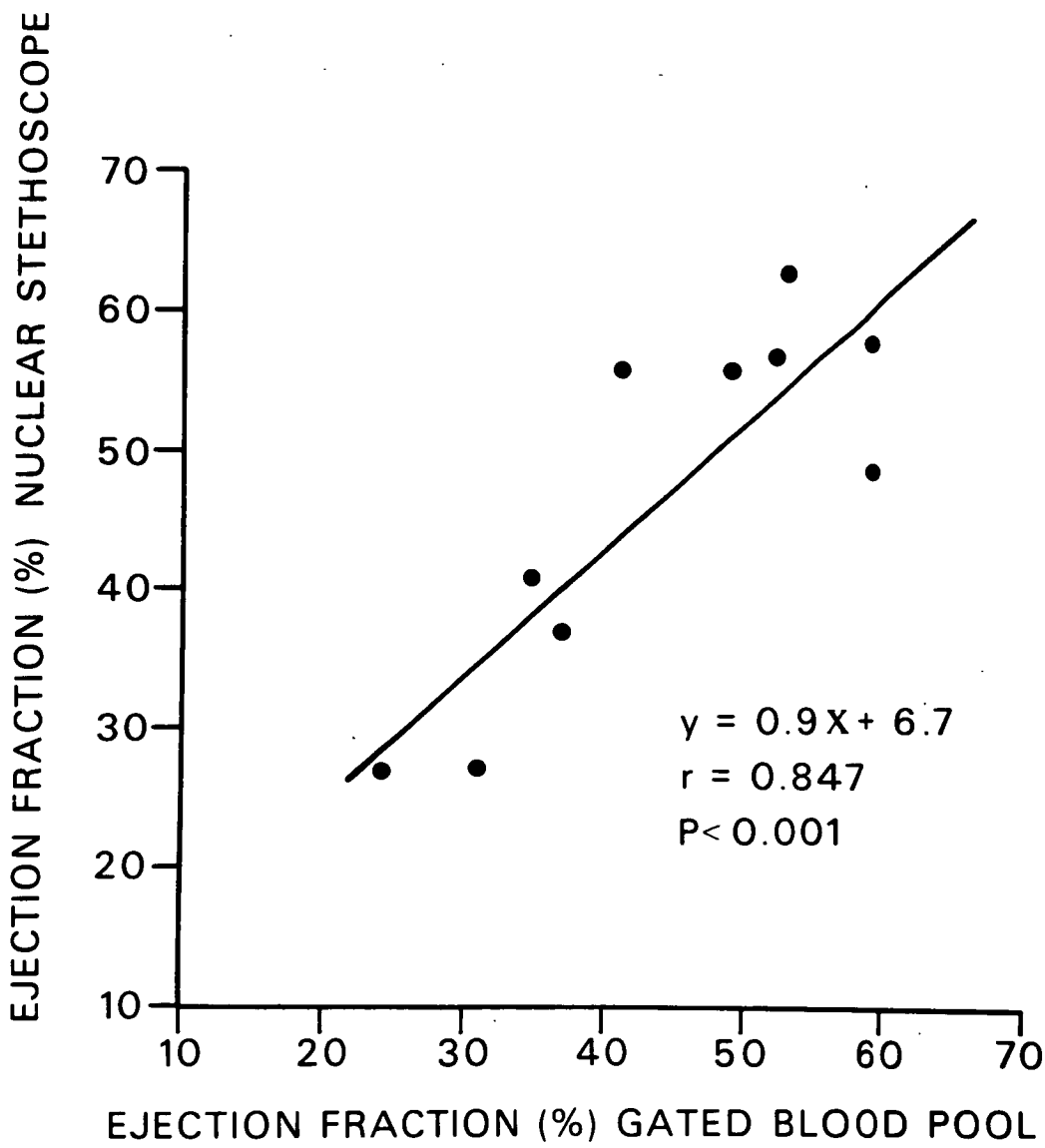
B. Beat-to-beat time-activity curve at greatest excursion of the horizontal bar. (See text for full description).

FIG 3.3



This figure illustrates the "Ventricular Function Curve" recorded by the "Nuclear Stethoscope". It demonstrates a two minute recording of the time-activity curve gated for every second RR interval. A more detailed description is provided in the text.

FIG 3.4



Comparison of radionuclide ejection fraction determined by gamma-camera and "Nuclear Stethoscope".

3.5 M-Mode Echocardiographic Assessment of Left Ventricular Function:

This technique provides an alternative non-invasive method for measuring left ventricular dimensions during systole and diastole. By making several assumptions about ventricular shape, volume, and ejection fraction may be determined. It should be noted that for M-mode echocardiography assumptions are false when regional wall motion abnormalities are present thus volume and ejection fraction measurement is inaccurate.

Left ventricular chamber dimension can most accurately be assessed by echocardiography at a level between the papillary muscles and the free edge of the mitral valve. To standardise the procedure, the transducer is placed on the chest wall in that intercostal space which permits recording of the mitral valve leaflet when the transducer is perpendicular to the chest wall. By tilting the transducer inferiorly and slightly laterally, characteristic left ventricular echoes are seen, allowing highly reproducible quantitation of ventricular dimensions (Popp, 1979). Assuming a uniform geometric model for the ventricle, theoretical ventricular volume may be calculated from the single known left ventricular dimension. Techniques and equipment used in assessing patients with dilated cardiomyopathy are described in Chapter 9.

The technique was not used to assess left ventricular function in patients with ischaemic heart disease, as regional wall motion abnormalities are common in this condition.

3.6 Exercise Testing:

Although exercise testing has commonly been used in the diagnostic evaluation and follow-up of patients with angina pectoris, exercise has only recently been employed to assess the degree of functional limitation in patients with heart failure. Franciosa et al (1979) have found that the exercise test is better able to categorise patients with heart failure than physical examination or resting haemodynamic characteristics. Although Patterson et al (1972) demonstrated good overall correlation between NYHA Functional Classification and treadmill exercise tolerance, significant differences occurred in 25% of patients highlighting the subjective nature of historical classification. Furthermore, recent studies in patients with heart failure have shown that physical findings, chest films, echocardiograms and resting haemodynamics are inconsistently altered by therapeutic interventions which do increase exercise capacity (Franciosa et al, 1978; Awan et al, 1977; Aronow et al, 1977). Thus, exercise capacity has become another important parameter in assessing the severity of heart failure, as well as the response to treatment.

In the studies incorporated in this thesis, exercise tests were performed on a bicycle ergometer (Elma-Schonander Ergometer EM 369) or treadmill (Quinton Model 643) using various progressive, multi-stage protocols. These varied with each study, thus the protocol employed will be outlined at the appropriate time. All patients exercised until the onset of dyspnoea or fatigue, and no-one stopped because of chest pain, arrhythmia or electrocardiographic changes. While exercising, patients were frequently asked whether they felt too breathless or tired to continue. They were given reassurance and encouraged to continue as long as objective parameters and my assessment indicated that it was safe to do so. Before commencing any trial, patients underwent an exercise test so that they would be familiar with test procedures. Every attempt was made to standardise conditions for testing. The temperature of the study room was maintained fairly constant, and patients were studied at the same time of day, at least two hours after the last meal.

Franciosa et al (1979) and Patterson et al (1972) had previously demonstrated that maximal exercise testing could be safely carried out and was well tolerated in patients with heart failure. The electrocardiogram and heart rate were recorded continuously (Avionics Exer Stress Model 3000), while cuff blood pressure was measured every minute (Avionics "Pressurometer" Model 1905) and exercise was supervised by a physician throughout, usually by myself. An emergency trolley with defibrillator, emergency drugs and resuscitation equipment was on hand in case of emergency, however none arose during the exercise testing of patients in the following studies.

3.7 EVALUATION OF RESPIRATORY GAS EXCHANGE DURING EXERCISE:

The heart and lungs constitute the fundamental elements of the body's oxygen transport system. The cardiovascular and respiratory systems are functionally integrated into a single metabolic unit, the cardiopulmonary unit, to transfer oxygen from the atmosphere to the metabolising tissues at a rate commensurate with their needs. Heart failure has been defined according to a defect in oxygen delivery relative to the oxygen requirements of the tissues. In patients with severe cardiac failure, for example, such a defect may be apparent at rest, whereas in patients with less severe disease, the increased oxygen demand attendant with exercise is required to expose an abnormality in oxygen delivery. The aerobic capacity of the patient with cardiac disease will therefore be dictated by the adequacy of the cardiac reserve and the relationship between oxygen delivery and the prevailing oxygen demand.

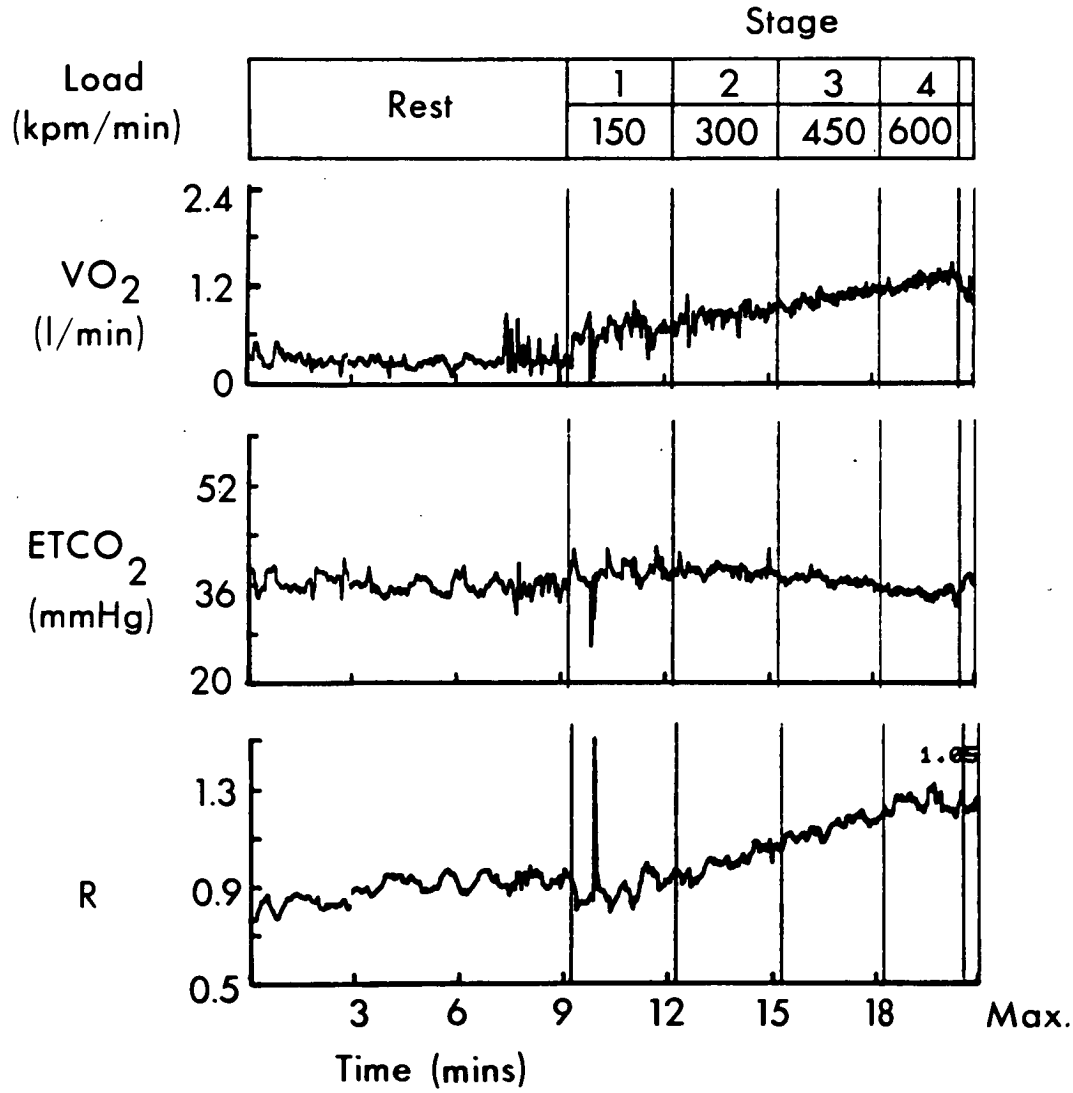
The severity of cardiac disease has traditionally been gauged by an analysis of historical information (see section 3.2) which the patient relates concerning the levels of exertion that are typically associated with the onset of breathlessness and/or fatigue. The severity of heart failure may be assessed more quantitatively by the response in oxygen delivery during exercise (Weber et al, 1982b). Thus, maximal aerobic capacity may be measured, and the adequacy of its measurement may be further enhanced by observing the onset of anaerobic metabolism (see below). The advent of rapidly responding gas analysers now facilitates the determination of these parameters during exercise.

Measurements of expired oxygen and carbon dioxide concentration (Mass spectrometer Perkin-Elmer MGA 1100) and air flow (Fleisch pneumotachograph) were made at rest and throughout exercise, using a breathing apparatus consisting of a mouthpiece, nose clamp, and low resistance Hans-Rudolf valve. Respiratory parameters were derived from gas concentration, flow and appropriate conversion factors for ambient temperature, barometric pressure, and water vapour.

On a breath-by-breath basis, derivations were performed on-line by a Digital PDP 11-10 Computer using software similar to that developed by Beaver et al (1973).

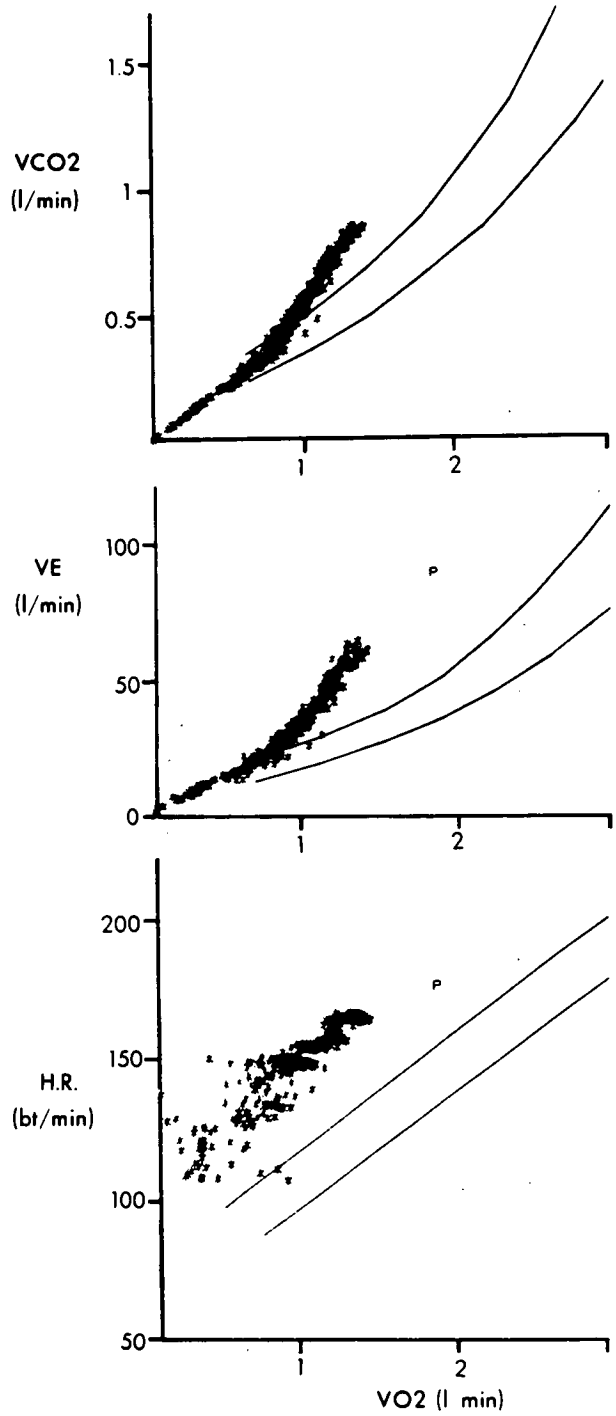
Oxygen consumption (V_{O2}, end-tidal carbon dioxide Concentration ($ETCO_2$) and respiratory quotient ($R=V_{CO2}/V_{O2}$) were displayed graphically during exercise (fig 3.5). The onset of anaerobic metabolism is heralded by the rise in respiratory quotient (Weber et al, 1982b). This is more clearly demonstrated by the disproportionate rise in ventilation and carbon dioxide production relative to oxygen uptake (fig 3.6). This results from impaired delivery oxygen to exercising muscles, with conversion to anaerobic metabolism and lactate production. The lactate is rapidly buffered by the body's bicarbonate pool, thus carbon dioxide production increases. Moreover, ventillation must rise more rapidly to maintain eucapnia (Weber et al, 1980). In heart failure, the V_{O2} to heart rate relationship is often abnormal as stroke volume is reduced, thus a higher heart rate is required to maintain oxygen delivery, thus the oxygen pulse V_{O2}/HR is often higher than normal, as seen in fig 3.6.

FIG 3.5



On-line graphical display of oxygen consumption (V_{02}), end-tidal carbon dioxide ($ETCO_2$) and respiratory quotient (R) - (see text for discussion).

FIG 3.6



Relationship between oxygen consumption (V_{O2}) and carbon dioxide production (V_{CO2}), ventilation (V_E) and heart rate. Normal values are those used by Jones et al (1975). The solid lines represent $\pm$ standard deviation from the mean values at each level of oxygen consumption.

CHAPTER 4

MEASUREMENT OF HAEMODYNAMIC PARAMETERS :

4.1 INTRODUCTION :

The advent of cardiac catheterisation in the last thirty to forty years has revolutionised clinical cardiology, improving diagnosis, management and understanding of the pathophysiological basis of cardiac disorders. With the realisation that left ventricular end diastolic pressure may be adequately assessed by measurement of pulmonary capillary wedge pressure, the development of the Swan-Ganz balloon-tipped catheter has enabled bedside assessment of intra-cardiac pressures. Positioning in the pulmonary artery eliminates the dangers of systemic embolisation from prolonged catheterisation of the left ventricle, thus allowing a patient to be monitored over a period of hours or days. Furthermore, the response to therapeutic manoeuvres may be observed. Coupled with these pressure measurements, the presence of a thermistor at the tip of the catheter permits the measurement of cardiac ouput by a thermodilution technique described below.

The use of haemodynamics in the assessment of the severity of heart failure and response to therapy has already been discussed in the previous chapter. In this chapter, I outline methods of catheter insertion, intracardiac pressure and cardiac output measurements. Forearm plethysmography using a mercury-in-rubber strain gauge was utilised in the studies to be described in Chapters 6 and 7, so theory and methods will be discussed in section 4.6.

4.2 CATHETER INSERTION:

1. Patient preparation:

Most patients had already undergone diagnostic cardiac catheterisation prior to these studies, so they were familiar with the basic techniques. An adequate explanation of the procedure was satisfactory to allay fears and most patients did not require premedication.

2. Technique:

A Swan-Ganz balloon tipped, thermodilution catheter was inserted by Seldinger technique via the subclavian vein on the non-dominant side of the body. In studies lasting several hours, the catheter was inserted through the median cubital vein. The catheter was advanced, under fluoroscopic control, to the right atrium where the balloon was inflated, then advanced through the right ventricle, and main pulmonary artery to the wedge position, usually in the right lower lobe artery. Pulmonary capillary wedge pressure was recorded, then with deflation of the balloon, the catheter recoiled into the main pulmonary artery where pressure was also recorded. In long-term studies, where the risks from distal migration of the tip are greater, the catheter was withdrawn into the main pulmonary artery if the mean pulmonary capillary wedge pressure and pulmonary artery end-diastolic pressure differed by less than 5 mm Hg (see section 4.3). The electrocardiogram was monitored continuously for early diagnosis of ventricular dysrhythmias that may be induced by passage of the catheter through the right ventricle.

For measurement of arterial pressure, the non-dominant radial artery was cannulated by direct puncture or the brachial artery was cannulated by Seldinger technique. Because the catheters remained in-situ for prolonged periods of time they were flushed at half-hourly intervals using heparinised dextrose (500ml 5% Dextrose and 2000 units heparin) to prevent obstruction of the lumen.

Standard flushing sets were used to facilitate this procedure and reduce the risk of infection. Despite these precautions, partial obstruction of the Swan-Ganz catheter lumen occurred on one occasion with resultant damping of pulmonary artery pressure, necessitating replacement of the catheter.

3. Ethical considerations have already been considered in Chapter 2.

4.3 PRESSURE MEASUREMENT :

1. General:

The measurement of arterial and intracardiac pressure is an important facet in assessing myocardial function. Arterial pressure is the most easily measured index of myocardial contractile force, while left ventricular end-diastolic pressure is used as an index of end-diastolic volume or cardiac "preload".

Pressure changes at the tip of the catheter, transmitted through the fluid-filled lumen displace the metal diaphragm of an externally placed transducer. This displacement results in a change of resistance, which can be measured accurately with a Wheatstone bridge circuit and displayed on an appropriately matched recorder.

2. Equipment:

Two pressure recording systems were used in the studies to be described:

1. Statham P28 transducer and DR8 Multichannel Recorder (Chapter 7);
& 2. Two Statham P50 transducers linked to a Mennen Medical monitor and Yokagoma E.W. (2932) photorecorder on a mobile trolley.

3. Zero Pressure and Positioning of Transducer:

All intracardiac pressures were measured relative to atmospheric pressure. Before each recording, the transducer was connected to air to ensure zero pressure. Positioning of the transducer relative to the heart is essential as a vertical displacement of 1.36 cm produces an apparent variation in pressure of 1 mm Hg due to gravity (SG of mercury = 13.6). The mid-axillary line, fifth intercostal space was taken as the reference point as this represents the approximate position of mid left atrium.

It should be noted that pressure inside a heart chamber need

not necessarily represent true transmural pressure, due to normal negative intrathoracic pressure which ranges between 0 and -8 mm Hg during normal respiration. To reduce the effect of this factor, all intra-cardiac pressures were measured when a breath was held at the end of normal expiration.

4. Calibration:

Known pressures were applied by means of a mercury manometer to the transducer producing displacement of the signal on the chart recorder which could be measured. Calibration was performed twice daily, and equipment was left turned on throughout each study day.

5. Representative Traces:

1. Arterial pressure:

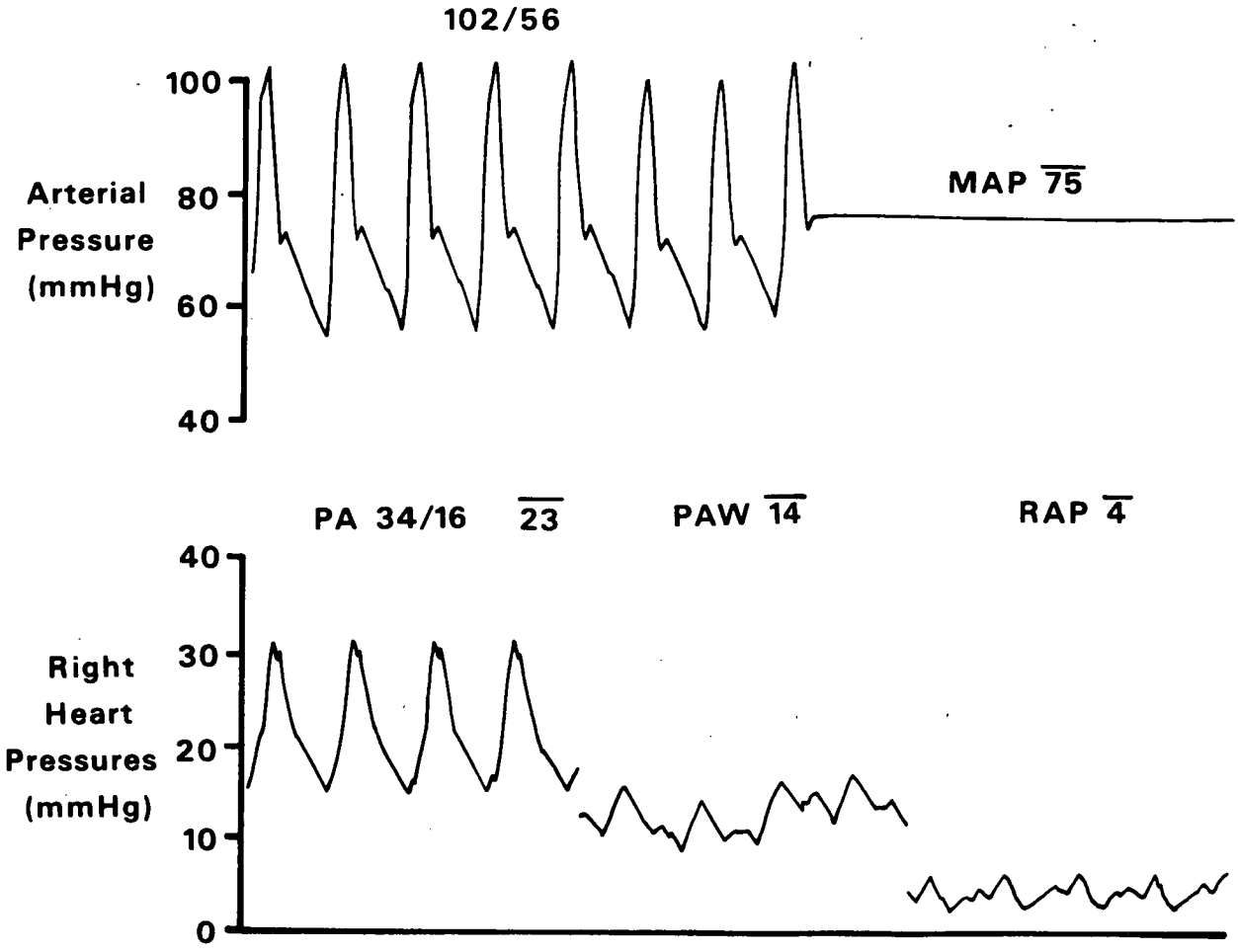
This tracing (fig 4.1) consists of a systolic wave, followed by the incisura, which denotes closure of the aortic valve, and then gradual fall in pressure during diastole as blood flows from the aorta to the capillary beds. Arterial pressure was measured at the peak of systole and at end diastole. Mean arterial pressure was determined by electronic integration.

Due to resonance within the arterial system, a wider pulse pressure may be measured from a brachial or radial artery than from central aortic pressure, while mean pressure may be identical or up to 5 mm Hg lower than central aortic pressure (Barry and Grossman, 1980). During the studies to be described, greater emphasis is placed on temporal changes than on absolute values, so these effects were of no consequence.

2. Pulmonary Artery Pressure:

Wave forms are similar to arterial pressure tracings with systolic, diastolic, mean pressures measured in an identical

FIG 4.1: REPRESENTATIVE PRESSURE RECORDINGS:



See text for description. MAP = mean arterial pressure, PA = pulmonary artery pressure (systolic, diastolic, and mean), PAW = mean pulmonary artery wedge pressure (capillary wedge pressure), RAP = mean right atrial pressure. Mean pressures were derived by electronic integration.

fashion. Motion of the catheter within the heart and great vessels accelerates the fluid contained within the catheter. Such catheter whip artifacts can produce superimposed waves up to ± 10 mm Hg (Barry & Grossman, 1980). They are particularly common in tracings from the pulmonary artery and are difficult to avoid. Fortunately this artifact occurred infrequently, but when present generally persisted unaltered for the duration of the study so its effects on pressure measurement were neglected, except that pulmonary artery wedge pressure was measured directly rather than assessed by measuring pulmonary artery end-diastolic pressure.

3. Pulmonary Capillary Wedge Pressure:

By inflation of the balloon at the tip of the Swan-Ganz catheter, the pulmonary artery within which it lies is occluded. Pressure at this point is similar to left atrial pressure, has a similar wave form but a and v waves are damped and delayed. Display of a representative wave form was essential (fig 4.1) before mean pressure was determined, again by electronic integration.

Under most circumstances, pulmonary artery flow is diminished at end-diastole, so that end-diastolic pulmonary artery and mean pulmonary capillary wedge pressure are approximately equal. Following catheter insertion, these pressures were compared. If they differed by less than 5 mm Hg, the catheter was withdrawn into the main pulmonary artery and pulmonary artery end-diastolic pressure was used as an estimate of left atrial pressure. For longer studies, this was necessary to reduce the risk of prolonged catheterisation from distal migration of the tip which may cause pulmonary infarction or rupture of a pulmonary artery.

4. Right Atrial Pressure:

Care was taken to record an adequate wave form (fig 4.1), then mean pressure was determined by electronic integration.

6. Effect of heart rhythm :

Atrial fibrillation commonly occurs in patients with heart failure. Variation in cycle length results in varying filling periods with consequent effects on beat-to-beat pressure. In the presence of atrial fibrillation, pressure measurements were made on as many pressure pulses as possible (greater than ten) and then averaged.

4.4 MEASUREMENT OF CARDIAC OUTPUT:

Of the numerous techniques devised over the years to measure cardiac output, three have won general acceptance in cardiac catheterisation laboratories: thermodilution technique; Fick oxygen method; indicator-dilution technique. Each method requires cardiac catheterisation. Although several non-invasive methods have been developed, they do not appear to be sufficiently reliable for general use (Braunwald, 1980). Two methods were used in this thesis:

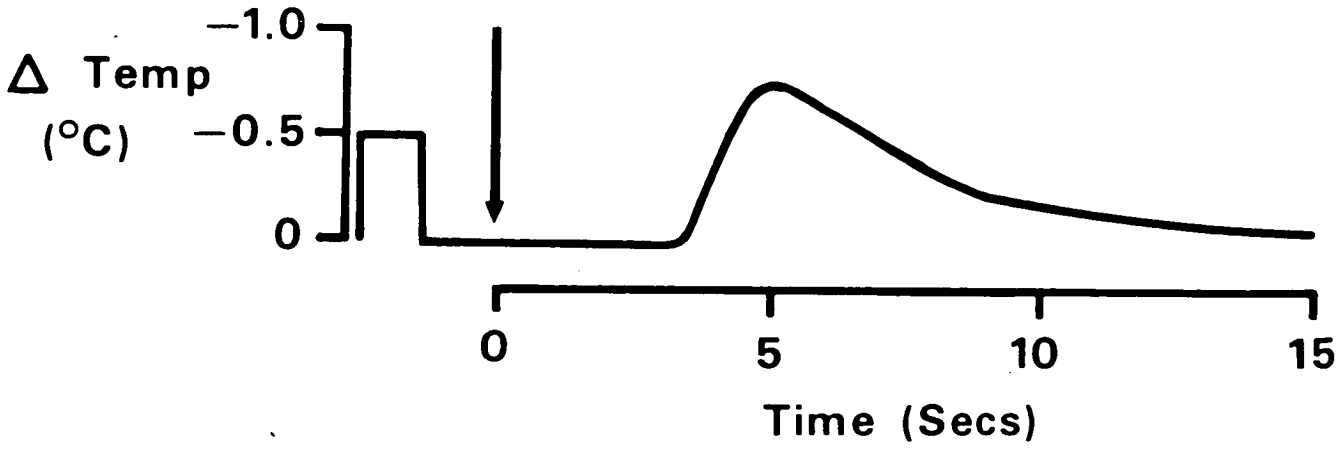
1. The Thermodilution Technique:

Of the three methods, the thermodilution technique has proved to be the easiest and most widely accepted method for repeated estimations of cardiac output. It avoids problems encountered with measurement of oxygen consumption and build-up of indocyanine-green dye. Ten mls of 5% dextrose cooled to 1-5^{o}C was injected through the right atrial port of the Swan-Ganz catheter. The temperature of the blood in the pulmonary artery was continuously monitored by means of a thermistor at the tip of the catheter. The area under the resulting curve (fig 4.2) was obtained by electronic integration, cardiac output was computed and the result rapidly displayed. Recordings were made in triplicate and averaged, while results with abnormal temperature-time curves or greater than 10% variation were excluded.

2. Fick Method :

This method is based on the theoretical principle, enunciated by Adolph Fick in 1870, that the total uptake or release of any substance by an organ is the product of blood flow to the organ and the arteriovenous concentration difference of the substance. For the lungs, the substance released to the blood is oxygen, and the pulmonary blood flow (cardiac output where a shunt is not present) can be determined by measurement of the arteriovenous differences of oxygen across the lungs and the oxygen consumption (ml/min).

FIG 4.2: MEASUREMENT OF CARDIAC OUTPUT BY THERMODILUTION.



Temperature at the tip of the Swan-Ganz is recorded continuously. Initially, electronic calibration provides a pen-deflection = -0.5° C. Following injection of 10ml dextrose at 0-5°C into the right atrium, change in temperature in the pulmonary artery was recorded. By measuring the area under the curve, cardiac output may be determined:

$$CO = \frac{V_i p_i C_i (T_b - T_i) \times 0.82 \times 60}{p_b C_b \times \int_0^\infty \Delta D_b(t)dt \times K}$$

where, V_i = volume of injectate (ml); p_i = specific gravity of injectate; p_b = specific gravity of blood; C_i = specific heat of injectate; C_b = specific heat of blood; T_i = initial temperature of injectate (°C); T_b = initial temperature of blood (°C); 0.82 = empirical correction factor for indicator loss between end and tip of the catheter; K = calibration factor for the curve (°C/mm);and

$\int_0^\infty \Delta D_b(t)dt$ = area under the curve registered following injection of the thermal indicator.

When 10 ml of cooled 5% dextrose is used:

$$CO = \frac{534.6(T_b - T_i)}{\text{Area under curve} \times K}$$

Cardiac output is determined from the following formula:

$$\text{Cardiac output} = \frac{\text{oxygen consumption}}{\text{AV oxygen concentration difference}}$$

4.5 INDICIES DERIVED FROM FLOW AND PRESSURE MEASUREMENTS :

1. Cardiac Index (CI) = CO/BSA ($l/min/m^2$);
2. Stroke Index (SI) = CI/HR ($ml/bt/m^2$);
3. Stroke Work Index (SWI) = SI(MAP - RAP)x0.0136 ($g.m/m^2$);
4. Systemic Vascular Resistance (SVR) = 80(MAP - RAP)/CO ($dyne\text{-}sec\text{-}cm^{-5}$);
5. Pulmonary Vascular Resistance (PVR) = 80(MPA - LVFP)/CO ($dyne\text{-}sec\text{-}cm^{-5}$);
6. Work Product = HR x SAP.

Where CO = cardiac output, BSA = body surface area, HR = heart rate, MAP = mean arterial pressure, RAP = right atrial pressure, MPA = mean pulmonary artery pressure, LVFP = left ventricular filling pressure, SAP = systolic arterial pressure.

4.6 FOREARM PLETHYSMOGRAPHY :

1. General:

The measurement of volume changes in the limbs or in the portion of the limbs of man has been recognised as a valuable research tool since the beginning of the century (Hewlett & Van Zwaluwenburg, 1909). Volume plethysmography with venous occlusion became the standard method of estimating peripheral blood flow in man. This method, however, is cumbersome, time consuming, requires complete immobility and has many sources of error (Lansdowne & Katz, 1942).

In 1953, Whitney (1953) described a technique for the precise measurement of changes in girth with a mercury-in-rubber resistance strain gauge. The principle of this gauge is the effect of extension of a small bore rubber tube on the resistance of a mercury thread completely filling the bore of the tube. In the following paragraphs I will outline the theoretical and practical aspects of this technique, which was used in two studies.

2. The Technique:

A cuff is applied around the upper arm and inflated to 40 mm Hg. Arterial inflow is not affected, but venous return is blocked, thus the forearm increases by a volume equivalent to arterial inflow. The circulation to the hand is occluded by a cuff at the wrist which is inflated to 200 mm Hg one minute prior to inflation of the proximal cuff.

The proximal cuff which is 4 cm wide is connected by a short large bore tube to a pneumatic unit which contains a high rate compressor with two large buffers which allows for extremely rapid cuff inflation, thus avoiding blood leakage from the very start of venous occlusion. The mercury-filled strain gauges have a 0.6 mm external diameter and a bore of 0.3 mm. They are very elastic, with as little as 200 mg force causing a 1% elongation. Their internal

electrical resistance varies in a linear fashion with elongation to 50% of the initial value. Changes in resistance and hence length can be measured accurately using a Wheatstone Bridge. Calibration of the strain gauge is independent of initial elongation and performed electronically to produce a pen deflection of $\Delta V/V = 1\%$ (see fig 4.4).

3. Theoretical Aspects:

The percentage change in volume is related to the percentage change in girth if the following assumptions are made:

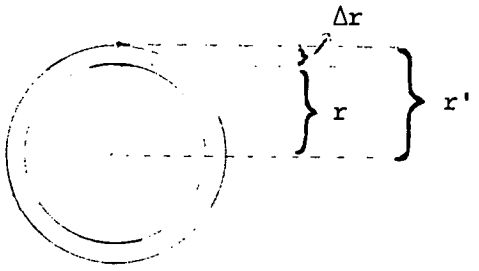
1. The length of the limb remains unaltered during volume changes;

2. The transverse sectional shape remains unaltered during volume changes;

3. The volume change is small when compared with the initial volume.

It is not necessary to assume that the arm is circular but the mathematics of the relationship between girth, area and volume changes are easier to demonstrate (fig 4.3). More complex mathematics summing narrow triangular elements (Whitney, 1953) show that the relationship holds true for ellipses if assumption 3 is correct.

FIG 4.3: RELATIONSHIP BETWEEN GIRTH, AREA, AND VOLUME CHANGES:



r = radius

G = girth

A = area

V = volume

$$G = 2\pi r$$

$$\Delta G = 2\pi r' - 2\pi r$$

$$\therefore \frac{\Delta G}{G} = \frac{r' - r}{r} = \frac{\Delta r}{r} \qquad \text{.....1}$$

$$A = \pi r^2$$

$$A' = \pi r'^2$$

$$\therefore \frac{\Delta A}{A} = \frac{r'^2 - r^2}{r^2} = \frac{r^2 + 2r\Delta r + \Delta r^2 - r^2}{r^2}$$

$$= \frac{2r\Delta r + \Delta r^2}{r^2}$$

When Δr is small compared to r and using equation 1:

$$\frac{\Delta A}{A} = \frac{2\Delta r}{r} = 2\frac{\Delta G}{G} \qquad \text{.....2}$$

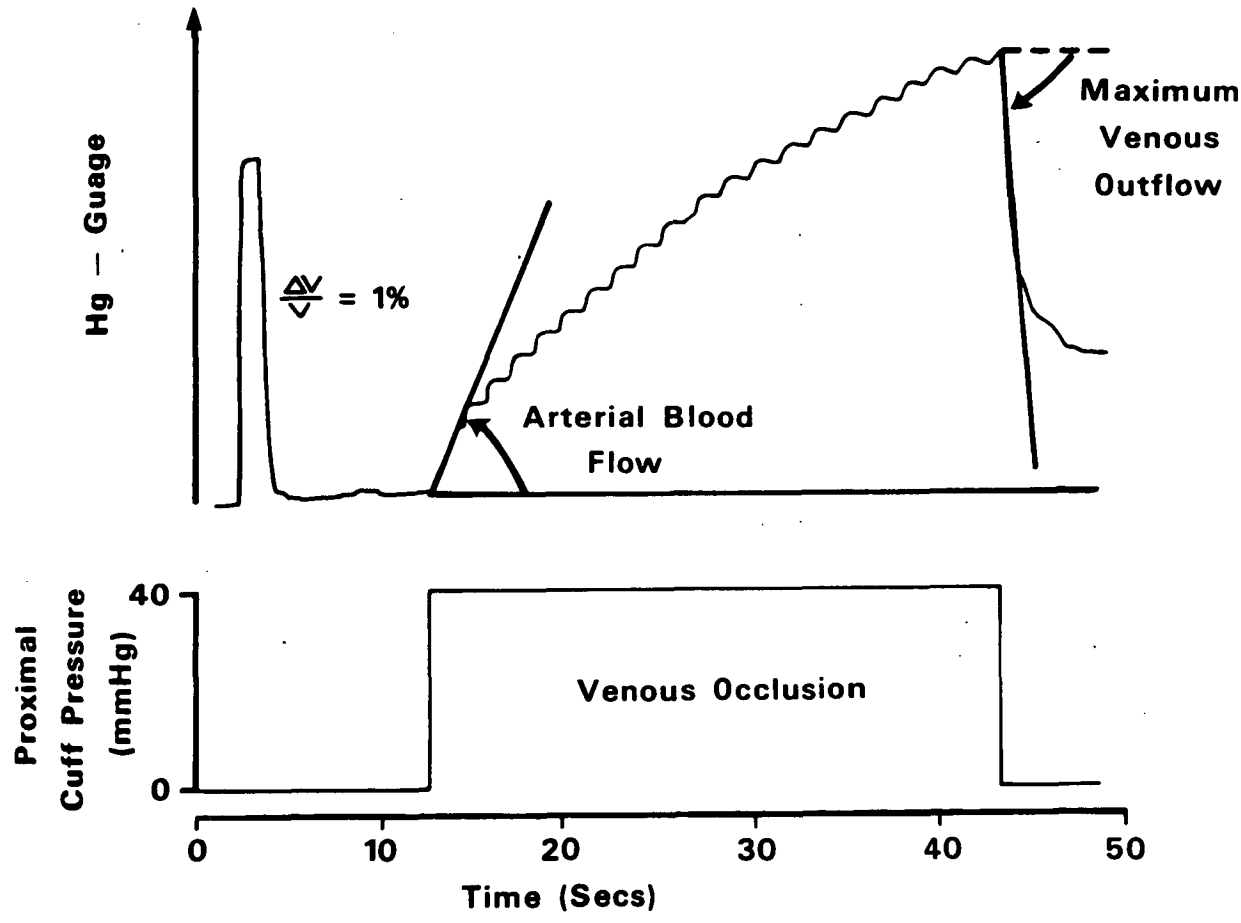
Taking assumption 1 and using equation 2:

$$\frac{\Delta V}{V} = 2\frac{\Delta G}{G}$$

4. Forearm Blood Flow Measurements:

A representative recording is shown in fig 4.4. The initial calibration pulse provides $\Delta V/V = 1\%$. After establishing a stable baseline the proximal cuff was inflated to 40 mm Hg. Initially arterial inflow is not affected, but venous return is blocked. Thus the limb segment increases by a volume equivalent to arterial inflow, which can be calculated from the slope of the asymptote and has the units of ml/min/100g of tissue. As the venous pressure rises, blood flow declines and limb segment volume forms a plateau. With rapid deflation of the proximal cuff, maximum venous outflow may be calculated in a similar manner to arterial flow. Recorded values represent the mean of five determinations with less than 10% variation taken at least three minutes apart.

FIG 4.4: FOREARM BLOOD FLOW MEASUREMENTS:



See text for description.

CHAPTER 5

HORMONE ASSAYS AND METABOLIC BALANCE:

5.1 GENERAL:

Hormone assays are essential for the diagnosis and management of most endocrine disorders. Until the last decade, only a limited range of hormone assays was widely available. With the advent of improved techniques, especially radio-immunoassay, a large number of hormones may now be assayed, these methods being simpler, cheaper and more sensitive than previous methods. Research has blossomed into poorly understood hormone systems - their physiological and clinical relevance. Elucidation of the role of the renin-angiotensin-aldosterone system, circulating catecholamines and antidiuretic hormone in heart failure is no exception.

Correlation of hormonal with haemodynamic indices in heart failure under control conditions and following therapeutic intervention forms the basis of three studies reported in this thesis. In this chapter, I outline assay techniques for each hormone measured. Detailed discussion of the relative merits of different assays, however, is beyond the scope of this thesis.

Many biological variables influence hormone levels (table 5.1), thus conditions under which the studies reported in Chapters 6 to 8 were carefully controlled. Patients remained at rest, in the semi-supine position throughout the period of investigation, with constant sodium and potassium intake, and with free water intake. Blood samples were drawn in the fasting state (0830) and at other times of the day, these times being held constant so that direct comparisons could be made. Apart from the medication under investigation, all other drug therapy was constant throughout the study, administered at the same time each day and minimised to reduce hormone inter-reactions. Meals were served at the same time each day as digestion has definite haemodynamic and metabolic consequences (Grollman, 1929).

TABLE 5.1 : SOME FACTORS AFFECTING HORMONE LEVELS :

Biological variable	Hormones affected
Body Posture	RAAS, Catecholamines, ADH
Stress	Cortisol, Catecholamines
Circadian rhythm	Cortisol, Aldosterone, Renin
Dietary Na and K	RAAS, Catecholamines
Drugs	Many
Fasting	Metabolic hormones
Hydration	Antidiuretic hormone

RAAS = renin-angiotensin-aldosterone system

The assays were developed in the Department of Endocrinology and have been used clinically and experimentally for many years. Normal values in healthy volunteers on unrestricted diets are given in Table 5.2. Quality control was checked by the biochemist Dr. Yandle (Ph.D.) and at two weekly intervals by Prof. Espiner and Dr. Nicholls (endocrinologists).

Many hormones (eg. angiotensin, ADH, catecholamines) are unstable in blood. For this reason, blood samples were drawn into appropriate chilled tubes, carried on ice to a cold room, and centrifuged immediately. The plasma was then frozen and stored at an appropriate temperature within 30 minutes of sampling. To avoid inter-assay variation, all samples for each patient were stored and assayed together.

5.2 PLASMA ANGIOTENSIN II: (Nicholls & Espiner, 1976)

Blood samples were drawn into chilled tubes containing an inhibitor solution of O-phenathroline, EDTA and neomycin to prevent enzymatic and bacterial breakdown of angiotensin II. They were then centrifuged and stored in a manner already described.

Following initial thawing, denaturation and precipitation of protein by ethanol to remove interference with angiotensin binding, the supernatants were dried and analysed using a radioimmunoassay technique. Optimal amounts of anti-serum and labelled (I^{125}) angiotensin had previously been determined to produce 50% binding when no "cold" angiotensin II was present. The anti-serum used did not significantly cross-react with angiotensin I, but did exhibit 100% cross-reactivity with the hexa and heptapeptide breakdown products of angiotensin II. Once antiserum and tracer were added, samples were incubated at $4^{o}C$ for 24 hours. The AB-AG complex was then separated from free angiotensin II by addition of dextran-coated charcoal solution. After centrifugation, the supernatant was discarded and counts from the charcoal deposit were measured in a scintillation counter.

A standard curve (fig 5.1) was constructed from concurrently run analyses of known concentrations of pure angiotensin II (Beckman Ltd.) diluted in human serum albumen. Sensitivity was enhanced by adjusting antiserum and tracer quantities to place expected plasma angiotensin II levels on the steep portion of the standard curve. The lower limit of detection was around 4 - 5 pmol/l (with some variation between assays). Excessively high samples were diluted and analyses repeated. When antiserum was not present, non-specific binding of tracer averaged 3%. The interassay coefficient of variation for the assay was in the range of 8 - 15% while intra-assay variation amounted to 6 - 12%. These were slightly variable over time, but quite acceptable.

Legend for Figure 5.1:

$$I^{125}\text{-AII} + AB \rightleftharpoons I^{125}\text{-AII-AB}$$

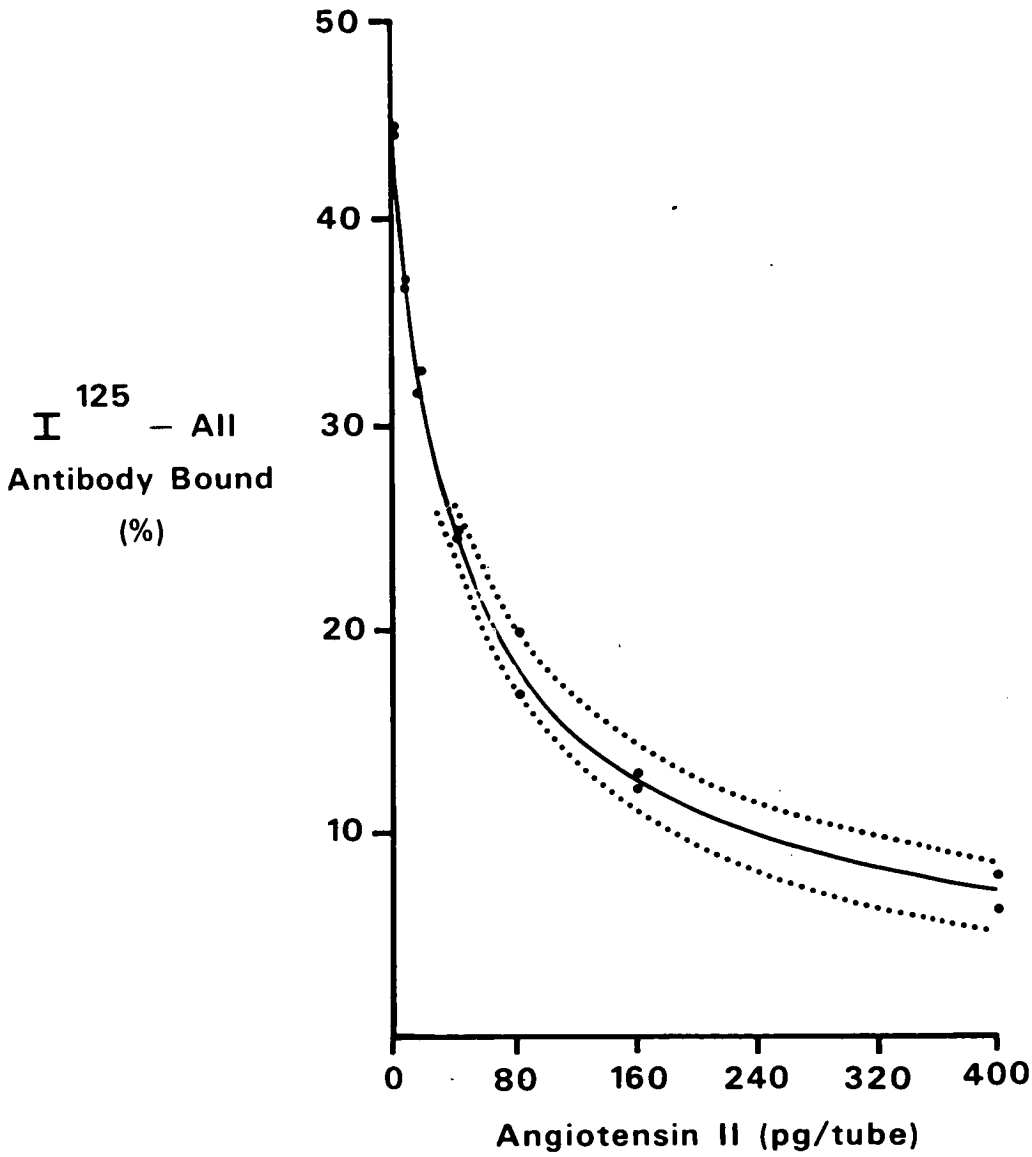
In the absence of "cold" angiotensin II (AII), binding of I^{125}-AII tracer ("hot" AII) was predetermined to be approximately 50%. Adding known amounts of "cold" AII reduced the binding of tracer to the antibody (AB), the standard curve could be constructed with the aid of a computer. Unknown plasma AII levels could then be determined by measuring the reduction in tracer binding. Accuracy was maintained by use of the steep portion of the curve and computer-aided transformation of the curve to a straight line.

* Values for binding at each known concentration of AII (measured in duplicate).

——— Represents the working range of the curve.

····· Represents the 95% confidence limits for duplicate measurements.

FIG 5.1: STANDARD CURVE FOR ANGIOTENSIN II RADIOIMMUNOASSAY



5.3 PLASMA RENIN ACTIVITY: (Dunn & Espiner, 1976)

Blood samples were collected into tubes containing EDTA, centrifuged and stored as already outlined. Storage at -20°C did not effect enzymatic activity. Samples were subsequently thawed and proteolytic enzyme inhibitors (dimercaprol and hydroxyquinoline) added to prevent breakdown of angiotensin I. Neomycin was added to the buffer to prevent bacterial degradation, and pH was set at 7.4. Samples were incubated for three hours in a water bath at 37°C in duplicate, and also at 4°C for determination of baseline levels of angiotensin I. It should be noted at this point that the pH for the 37°C incubation step remains controversial, with many laboratories using a pH of 5 - 6 when enzymatic activity is greatest. However, a pH of this range is considered by some to be non-physiological. The important point is that the pH chosen was adhered to throughout, and in our laboratories pH was buffered to 7.4.

Angiotensin I contents in both the 37°C and 4°C incubation tubes were measured by a radioimmunoassay technique using a specific antibody to angiotensin I. This technique is similar to that used for angiotensin II, with a standard curve produced in an identical fashion. Plasma renin activity, as estimated by the amount of angiotensin I generated in a given time, was the mean of the difference in angiotensin I between the tubes incubated at 37°C and the tube at 4°C. Wide variation in plasma renin activity between different plasma samples was often encountered, so dilutions of 1:3 and 1:8 were incubated and assayed simultaneously to allow use of the optimum portion of the standard curve. Occasionally very high levels of plasma renin activity were encountered requiring greater dilution and reassay on a subsequent day. Plasma renin activity not only depends on renin content, but also the presence of substrate (angiotensinogen) which is present in excess in most patients except those with hepatic failure or those with exceedingly high renin levels.

Intra- and interassay variation was 6.8% and 8.9% respectively. For higher levels inaccuracy was probably greater.

5.4 PLASMA ALDOSTERONE: (Lunn et al, 1983)

Plasma aldosterone was measured by a direct radioimmunoassay technique using a highly specific antiserum (St. Bartholomew's Hospital, London) exhibiting very low cross-reactivity with other steroids. 100 µl of plasma was mixed with optimal amounts of antiserum, buffer and I^{125}-histamine-aldosterone. Following incubation at 4°C for 20 to 48 hours, free aldosterone was separated from the AB:AG complex by the addition of dextran coated charcoal buffer and centrifugation. Percentage binding of tracer was calculated, thus plasma aldosterone could be determined from a concurrently derived standard curve constructed from known amounts of pure aldosterone diluted in charcoal stripped plasma.

The assay is sensitive with a good intra- and interassay coefficient of variation (8% and 10% respectively). The lower limit of detection is 10 pmol/l, which is well below the normal range of 140 - 550 pmol/l.

5.5 URINE ALDOSTERONE EXCRETION: (Nicholls et al, 1974)

Aldosterone is excreted in three main forms:

1. free aldosterone (0.2%);
2. aldosterone-18-glucuronide (15%);
3. tetrahydroaldosterone (40%);

while the remaining forms cannot be detected by current techniques. As it is difficult to measure quantitatively the amount of tetrahydroaldosterone excreted in the urine, the method used in these studies quantified aldosterone liberated from the acid-labile conjugate (aldosterone-18-glucuronide) by hydrolysis at pH 1. Preliminary extraction procedures included the removal of other steroids with methylene dichloride (as they are less polar), and removal of bile salts with sodium hydroxide. Further separation was then performed by paper chromatography.

Radioimmunoassay was performed using predetermined amounts of antiserum (kindly donated by the National Institute of Health, Bethesda Maryland, USA) and I^{125}-labelled aldosterone. Following incubation at $4^{o}C$ overnight, free and bound aldosterone were separated by the addition of saturated ammonium sulphate followed by centrifugation. Percentage binding of tracer was determined for unknown samples as well as for concurrently run known amounts of aldosterone. From the standard curve, recovery factor and total volume of urine collected, aldosterone excretion per 24 hours could be calculated. The test is sensitive, and has an interassay variation of 10% and intra-assay variation of 8% at high values (100 mmol/day) and 12% at low values (5 mmol/day).

5.6 PLASMA AND URINE CORTISOL:

Plasma and urine cortisol levels were measured by a direct radioimmunoassay method using antiserum highly specific for cortisol while exhibiting low cross-reactivity with other steroids (Diagnostic Products Corp). 25 µl of plasma were mixed with optimal amounts of antiserum, and I^{125}-labelled cortisol, then incubated at 37°C for 45 minutes. Urines were handled in a similar fashion, except that an initial extraction stage was added. 500 µl of urine were mixed with dichloroethane, centrifuged, then the supernatant was removed. Following evaporation, a calibrator fluid containing no cortisol was used to dissolve cortisol remaining in the tubes.

After incubation with antiserum and labelled cortisol, free and bound cortisol were separated by addition of an antibody specific for the cortisol antiserum, and centrifugation. Percentage binding of the tracer was calculated for unknown samples along with concurrently run known samples. From the standard curve, unknown concentrations of plasma and urine cortisol could be determined.

For plasma cortisol, the lower limit of detection was 17 nmol/l, which is well below the normal range (110-830 nmol/l). Intra- and interassay variation was less than 4% and 8% respectively.

5.7 PLASMA CATECHOLAMINES: (Peuler & Johnson, 1977)

Plasma norepinephrine and epinephrine were measured simultaneously using a radioenzymatic method. Thawed plasma (50 µl) was incubated for one hour (37°C) with catechol-o-methyl transferase (rat liver extraction, harvested locally) and tritiated-S adenosyl-L methionine (purchased from New England Nuclear Company). During incubation, norepinephrine is converted to H^3-normetanephrine, while epinephrine is converted to H^3-metanephrine. After several extraction steps using toluene and acetic acid, thin layer chromatography was performed (using an automatic multispotter) to separate the labelled normetanephrine and metanephrine. The site of these two products on the chromatography plates was then distinguished by ultra-violet light. The spots thus separated were removed from the plate and counted overnight in a scintillation counter. Counts from the sample are compared with counts from a blank, and a sample plus standard (100pg norepinephrine and epinephrine) which have undergone all steps of the method. Catecholamine concentration is determined by the following formula:

$$\text{Catechol. Conc. (pg/ml)} = \frac{\text{CPM(sample)} - \text{CPM(blank)}}{\text{CPM(sample + standard)} - \text{CPM(sample)}} \times \frac{\text{100pg(standard)}}{\text{sample volume (ml)}}$$

NB: (CPM = count per minute)

The assay is sensitive to a lower limit of approximately 25 pg/ml of epinephrine and norepinephrine, and exhibits 7 - 10% interassay variation. Very little crossover in the assay occurs between epinephrine and norepinephrine, however metabolites of isoprenaline and alpha methyl DOPA may interfere with the assay. Prenalterol added to plasma did not interfere with the assay.

5.8 Plasma Antidiuretic Hormone (ADH): (Saddler et al, 1983)

A sensitive assay for plasma ADH has recently been developed in the Department of Endocrinology (Sadler et al, 1983). For each sample, 5 ml of blood was drawn into tubes containing EDTA, centrifuged immediately at 4°C and plasma stored at -60°C until extraction and assay.

ADH was extracted from plasma by adsorption onto octadecasilyl-silica, then eluted with acetonitrile, acetic acid, dried under a stream of air at 37°C, then reconstituted in assay buffer. Radioimmunoassay for ADH was performed with buffer set at pH 7.4 and at 4°C. Standards consisted of nine doubling dilutions of synthetic ADH covering the range 0.1 to 32 pg. Duplicate aliquots (300 µl) of standards and triplicate aliquots of reconstituted plasma extracts were taken for assay. Samples were first incubated with specific rabbit antiserum (raised locally) for 48 hours. I^{125} labelled ADH (100 µl) and normal rabbit serum (1 µl) were added to all tubes and incubated for a further 24 hours. Antibody bound and free hormone were separated by the addition of donkey anti-rabbit gamma-globulin (Wellcome, UK) incubated for 20 hours, then centrifuged. Precipitates were counted for I^{125} activity and plasma ADH concentrations were calculated using a four parameter logistic function to represent the standard dose-response relationship.

The specificity of the hormone assay was good, with very low cross-reactivity with structurally similar hormones: oxytocin, angiotensin I and II, but greater with synthetic analogues: lycine vasopressin and glypressin. Intra-assay variation was 8%, while interassay variation amounted to 11%.

5.9: METABOLIC BALANCE

The aim of the dietary measures undertaken in the studies to be described, was to maintain a known, constant intake of sodium and potassium during the period of study. To minimise variations in the electrolyte content of the food, the projected requirements for each study was purchased in bulk and deep frozen, to allow the same stock to be used throughout. Following consultation with the patient concerning dietary preferences, a provisional diet sheet was prepared detailing the food items, their weight and estimated sodium and potassium content. A day's intake of food (including drinks) was pooled in a bucket, mixed with two to three litres of distilled water, and homogenised. From this, an aliquot of homogenate was taken for the determination of sodium and potassium concentration by flame photometry. Where necessary, adjustments to the diet regime were made if the measured electrolyte content differed significantly from that calculated by the dietician. On a few occasions, repeat analysis of the adjusted diet was made because of discrepancy between the initial calculated and analysed electrolyte figures.

For each 24 hour period of metabolic balance, the daily allowance of each food item was accurately weighed out. Cooking was carried out for a set time interval in the same amount of distilled water each day thus avoiding changes in electrolyte loss with cooking from day to day. Any food not eaten from one meal was retained and presented again with a subsequent meal on the same day, often in another form. If food was not eaten by the end of the 24 hour period, it was returned to the diet kitchen for weighing and estimation of electrolyte content. Fortunately, this was not a common occurrence. Despite the fact that the food presented to each patient was the same from one day to the next, patient acceptance was, in general, very good and few problems were encountered.

Urine was collected daily for estimation of sodium and potassium excretion. Thus, I was able to compare input and output of these electrolytes each day. Patients were deemed to be in "positive" balance if output was less than input for the measured interval, and vice versa

for "negative" balance. There are minor inaccuracies in estimating cumulative electrolyte balance from measurements of urine excretion alone, since small losses also occur in sweat and faeces, unless diarrhoea or excess sweating occurs.

TABLE 5.2: NORMAL LABORATORY VALUES:

PLASMA	
Plasma renin activity	0.15 - 2.7 nmol/l/hr
Angiotensin II	20 - 80 pg/ml (pmol/l)
Aldosterone	140 - 550 pmol/l
Norepinephrine	100 - 800 pg/l
Epinephrine	30 - 180 pg/ml
Cortisol	110 - 830 nmol/l
ADH	0.75 - 14.3 pmol/l
24 HR URINE:	
Aldosterone	10 - 60 nmol/day
Cortisol	100 - 500 nmol/day

NB. These ranges relate to values in normal healthy volunteers on unrestricted diets.

CHAPTER 6

ACUTE HAEMODYNAMIC, HORMONAL, AND ELECTROLYTE EFFECTS AND SHORT-TERM CLINICAL RESPONSE TO ENALAPRIL IN HEART FAILURE :

6.1 INTRODUCTION:

Oral angiotensin converting enzyme inhibitors have added a new dimension to long-term vasodilator therapy for heart failure (Hamer, 1982). Captopril, the only currently available oral angiotensin converting enzyme inhibitor, has been associated with potentially serious complications (Vidt, Brava, and Fouad 1982). Thus its use has been limited to those patients resistant to conventional therapy, in whom it has proved most effective (Maslowski et al, 1981a; Dzau et al, 1980). Enalapril (MK421) is a member of a new group of angiotensin converting enzyme inhibitors which lack mercapto function incriminated in the side-effects of captopril (Patchett et al, 1980). Preliminary data suggest that it is as effective and longer acting than captopril in hypertension (Gavras et al, 1981), and so far serious side-effects have not been encountered.

To date enalapril has not been assessed in heart failure. The purpose of this study was to document the haemodynamic, hormonal and electrolyte effects in patients with stable heart failure, and thereby evaluate the role of the renin-angiotensin-aldosterone system in this condition. Before discussing this study, it is pertinent to review the current role of vasodilator therapy in heart failure.

6.2 ROLE OF VASODILATOR THERAPY IN MANAGEMENT OF HEART FAILURE:

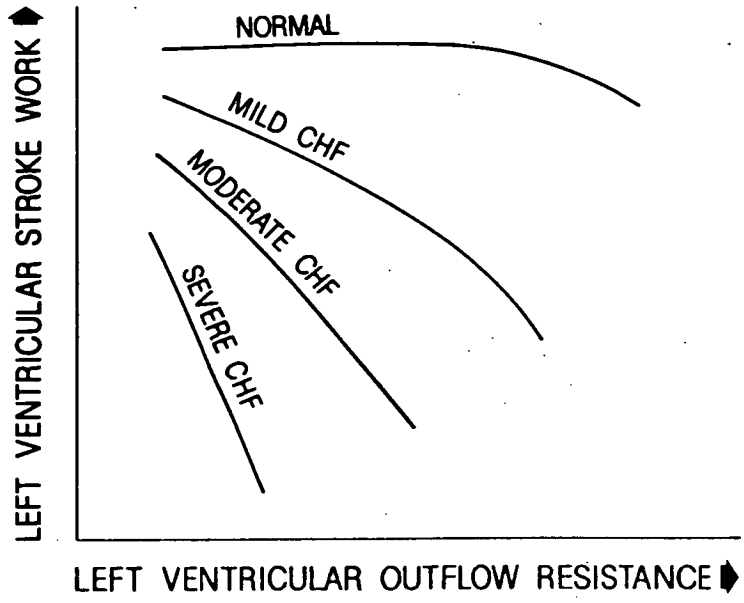
One of the major advances resulting from (and increasing our understanding of) haemodynamic studies and cardiac muscle mechanics is the concept of "afterload reduction" in heart failure (Zelis et al, 1979). Cohn et al (1963) demonstrated an increase in cardiac output in patients with heart failure who were treated with antihypertensive drugs. This response was initially attributed to the prevalent notion that the failing heart was operating on a descending limb of its Frank-Starling curve so that a reduction in filling pressure would increase cardiac output. Subsequently it became increasingly apparent that a descending limb of the Starling Curve probably did not exist except in the pre-terminal phase of severe heart failure.

Left ventricular outflow resistance, or impedance (or afterload), has been well known to physiologists as an important determinant of ventricular performance (Imperial, Levy, & Zieske, 1961; Sonnenblick & Downing, 1963). The normal heart maintains stroke volume relatively constant over a wide range of changes in resistance to outflow, but the failing ventricle becomes very sensitive to outflow resistance, such that an inverse relationship exists between stroke work and outflow resistance (fig 6.1). Reducing the increased outflow resistance in heart failure will increase cardiac output and this has been associated with symptomatic improvement (Franciosa, 1981).

Chronic heart failure can be looked on as a vicious cycle initiated by a cardiac lesion that impairs cardiac performance and results in reduced cardiac output (fig 6.2 taken from Franciosa, 1981). This low output may be initially compensated by activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, which ultimately elevates systemic vascular resistance. This further depresses ventricular performance, thereby completing a positive feedback loop. Conventional therapy often fails to significantly raise cardiac output or lower systemic resistance, in fact it may enhance vascular resistance (see Chapter 8), thus perpetuating the cycle.

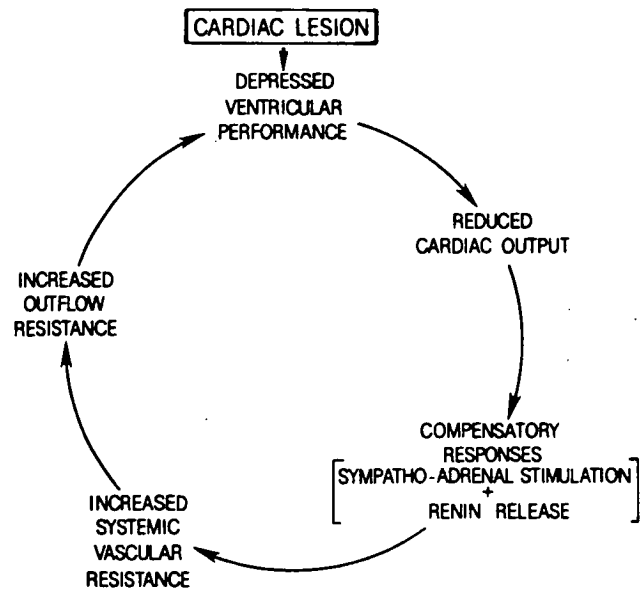
Agents that interrupt this cycle present a new therapeutic approach,

FIG 6.1 EFFECT OF AFTERLOAD ON CARDIAC FUNCTION:



This graph shows the relationship of left ventricular stroke work to the outflow resistance in the normal and failing ventricle. CHF = congestive heart failure (from Franciosa, 1981).

FIG 6.2: VICIOUS CYCLE OF HEART FAILURE: (From Franciosa, 1981)



many agents available in an oral form having been investigated. These include:

1. Direct vasodilators; eg. nitrates, hydrallazine
2. Alpha-adrenergic blockers; eg. prazosin
3. Beta-2 adrenergic agonists; eg. pirbuterol
4. Converting enzyme inhibitors; eg. captopril, enalapril.

There is little doubt that initial clinical improvement occurs in severely afflicted patients. There has, however, been some disappointment with the lack of sustained response in some patients, while others require an increase in diuretic dosage (Colucci et al, 1980a). With long-term prazosin therapy, plasma renin activity and plasma norepinephrine levels were increased (Colucci et al, 1980a; Cohn et al, 1978). From these findings, the researchers concluded that tolerance to vasodilator therapy results from enhanced sympathetic tone and activation of the renin-angiotensin-aldosterone system. Several researchers have found that the maximum arteriovenous oxygen difference during exercise is diminished suggesting that flow is directed away from exercising muscle (Moskowitz, Kinney & Zelis, 1978) thereby contributing to enhanced sympathetic tone in order to maintain blood flow to the exercising muscle. A rebound deterioration in condition occurs after withdrawal of most vasodilators due to the unopposed activation of these neurohumoral systems while on treatment. This phenomenon was not observed following withdrawal of long-term converting enzyme inhibition for four days (Maslowski et al, 1981b) and may be interpreted as showing lack of sustained effect. Deterioration in clinical and haemodynamic parameters did occur over one month (see Chapter 10) suggesting that four days was insufficient time for deterioration to occur. As discussed in Chapter 10, the vasodilator action of converting enzyme inhibitors does not appear to be opposed by activation of other neurohumoral systems.

Converting enzyme inhibitors appear to be emerging as the vasodilator of choice. They block the renin-angiotensin-aldosterone system which is thought to contribute most to the increased afterload in heart failure, especially in those patients on diuretic therapy who are sodium depleted relative to their effective blood volume (see Chapter

8). The predominant mechanism of action of converting enzyme inhibitors appears to be vasodilatation resulting from a reduction of plasma angiotensin II levels, while blockade of diuretic-induced hyperaldosteronism (Chapter 8) appears to be an added advantage for long term therapy. In the study reported in this chapter, I investigate the acute haemodynamic, hormonal and electrolyte effects along with the short-term clinical response to enalapril in nine patients in heart failure.

6.3 METHODS:

1. Patients:

Clinical details of the nine patients are summarised in Table 6.1. Vasodilators were withdrawn at least four days prior to the study, but digoxin (0.125 - 0.25mg/day) therapy was continued in unchanged dose throughout. Frusemide (table 6.2) was stopped four days before the study in three patients, while the other six were maintained on a constant dose during the in-patient period.

TABLE 6.1: CLINICAL DETAILS:

Patient	Age	Sex	Aetiology	Previous Vasodilators
1	57	M	DCM	Nil
2	58	M	IHD	Prazosin
3	62	M	DCM	Nil
4	59	M	IHD	Nil
5	48	M	IHD	Prazosin
6	70	M	DCM	Prazosin, Nitrates
7	48	M	IHD	Isosorbide Nitrate
8	61	M	IHD	Prazosin
9	66	F	IHD	Prazosin

DCM = dilated cardiomyopathy; IHD = ischaemic heart disease. Diuretic therapy, NYHA Functional class, and LVEF are listed in Table 6.2.

FIG 6.3: STUDY PROTOCOL:

Day 0	1	2	3	4	5
Insert Catheters (1600)	CONTROL PERIOD		ENALAPRIL (0900)		
			5mg	10mg	20mg
Haemodynamics & Hormones	A	B	B	A	A
24hr Urine Collection	*Electrolytes + Hormones*				
Diet	Constant Na 100mmol/day K 60mmol/day				

A = 0830, 1130, 1530hrs

B = 0830, 1000, 1100, 1300, 1500, 1700, 1900, 2100hrs

Catheters were inserted at 1600 hr on the day prior to commencing the study. The study consisted of a two day control period followed by three days of incremental daily doses of enalapril given at 0900 hr. Haemodynamic and hormonal measurements were made three times (A) on days 1, 4, and 5 and eight times (B) on days 2 and 3. Dietary sodium and potassium were held constant throughout, while daily urine collections were stored on ice for electrolyte, aldosterone, and cortisol excretion.

2. Study Protocol:

The protocol was approved by the Hospital's Ethical Committee, and all patients gave informed written consent. A dose finding study was performed on patient 1. In his case, enalapril was administered once daily (0900 hr) in increasing doses of 1.25, 2.5, 5 and 20mg. For the remaining eight patients, the protocol (fig 6.3) entailed a control period of two days followed by three days of incremental enalapril administration - 5, 10 and 20mg given at 0900 hrs on days 3, 4 and 5 respectively. Throughout the study and for two days prior to its initiation, each patient received a diet of constant sodium (91 - 116 mmol/day) and potassium (54 - 67 mmol/day) content. Meals were served at 0915 hr, 1215 hr and 1815 hr. All urine was collected on ice for electrolyte and hormone analysis. The patients remained semi-supine throughout. On the afternoon prior to day 1, a triple lumen Swan-Ganz catheter was placed in the pulmonary artery for right heart pressure and cardiac output measurements (see Chapter 4), and a brachial artery cannula was inserted for pressure recordings and blood sampling for hormone analysis.

In order to provide detailed information of first-dose effects, simultaneous haemodynamic and hormone recordings were carried out eight times on the first day of enalapril (5mg) treatment (fig 6.3), and for comparison at identical times on the preceding control (pre-enalapril) day. On all other study days, these measurements were performed at 0830 hr, 1130 hr and 1530 hr. Plasma was drawn at 0830 hr daily for sodium and potassium measurements (flame photometry), while plasma ADH levels were measured at 1130 hr daily. Digoxin and frusemide (in six patients) were taken immediately after the 0830 hr recordings.

In three patients, intra-arterial pressure and heart rate were measured continuously on the first day of enalapril treatment and for comparison on the preceding (control) day using a transducer unit, along with the ECG signal from chest leads, on a Medilog Mark 1 miniaturised tape recorder (Oxford Medical Systems - Millar-Craig,

Hawes, & Whittington 1978b). After visual editing of the tapes, digital hourly means for arterial pressure and heart rate were obtained.

After completion of the in-patient protocol, the subjects were discharged from hospital receiving enalapril 5 or 10 mg once or twice daily (table 6.2). Before the invasive study and again four to eight weeks after its completion (during continued enalapril therapy), patients were assessed by physical examination, New York Heart Association (NYHA) Functional Classification, maximum exercise capacity ("Naughton protocol" - Patterson et al, 1972) and resting technetium cardiac scan.

3. Statistics:

Repeated measures analyses of variance were performed for all variables. For indices exhibiting significant variation between days, further comparisons using t-tests with appropriate mean square error terms from analysis of variance were performed to determine when these changes occurred. Students t-test for paired samples was used to evaluate the chronic (four to eight weeks) effects of enalapril. Results are presented as mean $\pm$ standard error of mean (SEM).

6.4 RESULTS:

1. General:

All but one patient (μ 2) completed the acute protocol. This patient developed staphylococcus aureus septicaemia from a contaminated catheter on the final day, which responded rapidly to antibiotic therapy. His results are included in data analysis for the first dose effect of enalapril, and also for follow up since enalapril was reintroduced without complications. The pattern of hormone and haemodynamic response was similar in patients who continued frusemide treatment to those in whom diuretics had been withdrawn, thus all results have been combined.

2. Dose-finding study in Patient 1:

The effects of four different doses of enalapril on plasma renin activity and mean arterial pressure in patient 1 are shown in fig 6.4. It should be noted that chronic frusemide therapy (40 mg daily) was stopped four days before the study in this patient. From his data and preliminary data in hypertensives, a starting dose of 5 mg was selected. Results of hormone and haemodynamic measurements made in this patient are not considered further, but his follow-up data were analysed along with the data from the other patients.

3. Hormone Response:

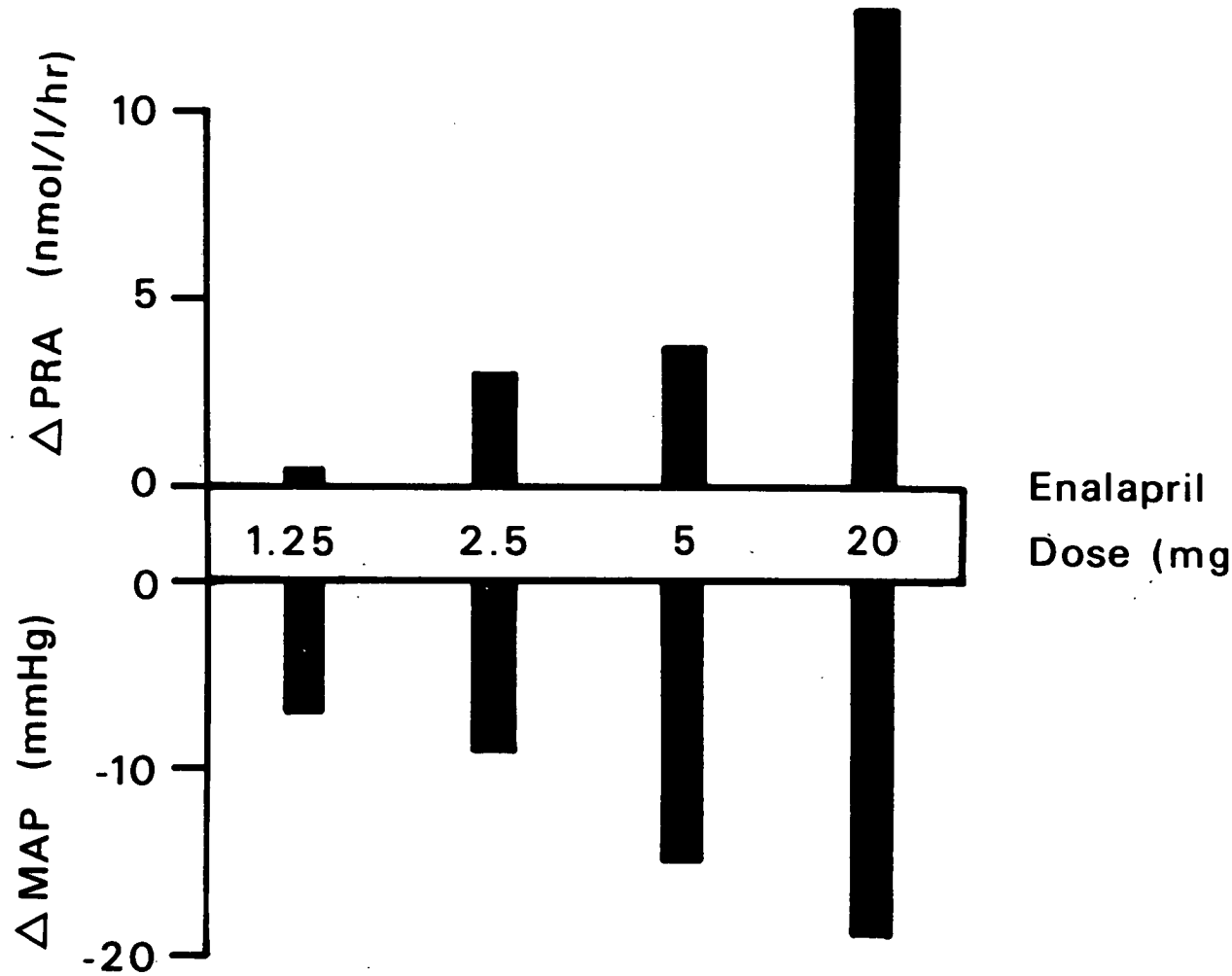
Angiotensin II levels were lower two hours after 5 mg of enalapril than at the same time (1100 hr) on the previous control day (58 $\pm$ 16 pmol/l compared to 81 $\pm$ 23 pmol/l, $p<0.05$). A nadir of 29 pmol/l occurred ten hours after the drug was administered, and remained 23 pmol/l below matching control levels at 24 hours ($p<0.05$). A reciprocal rise in plasma renin activity occurred, becoming significant four hours after 5mg of enalapril; reaching a peak which was four-fold higher than the time-matched control levels at six hours; then declining toward control values at twelve and twenty-four hours. Plasma aldosterone levels were not altered, but

it is noteworthy that baseline plasma aldosterone concentrations (360 ± 52 pmol/l at 0830 hr - thirty minutes before enalapril administration) were not elevated. Plasma norepinephrine levels four to twelve hours after enalapril tended to be lower than at the same time on the preceding control day, but only at eight hours was the difference statistically different (494 ± 58 pg/ml compared to 753 ± 198 pg/ml, $p<0.01$). Epinephrine and cortisol levels were not altered by enalapril.

Incremental doses of enalapril produced similar dose-related decrements in plasma angiotensin II and increments in plasma renin activity when 2.5 and 6.5 hour results were combined and also when 24 hour post-dose results were considered (fig 6.6). Although similar patterns were observed for plasma aldosterone and norepinephrine, the changes were not statistically significant. Presentation of data in this form was necessary as the duration of effect of the drug appeared to be greater than 24 hours, thus a baseline was not re-established before the next dose was administered.

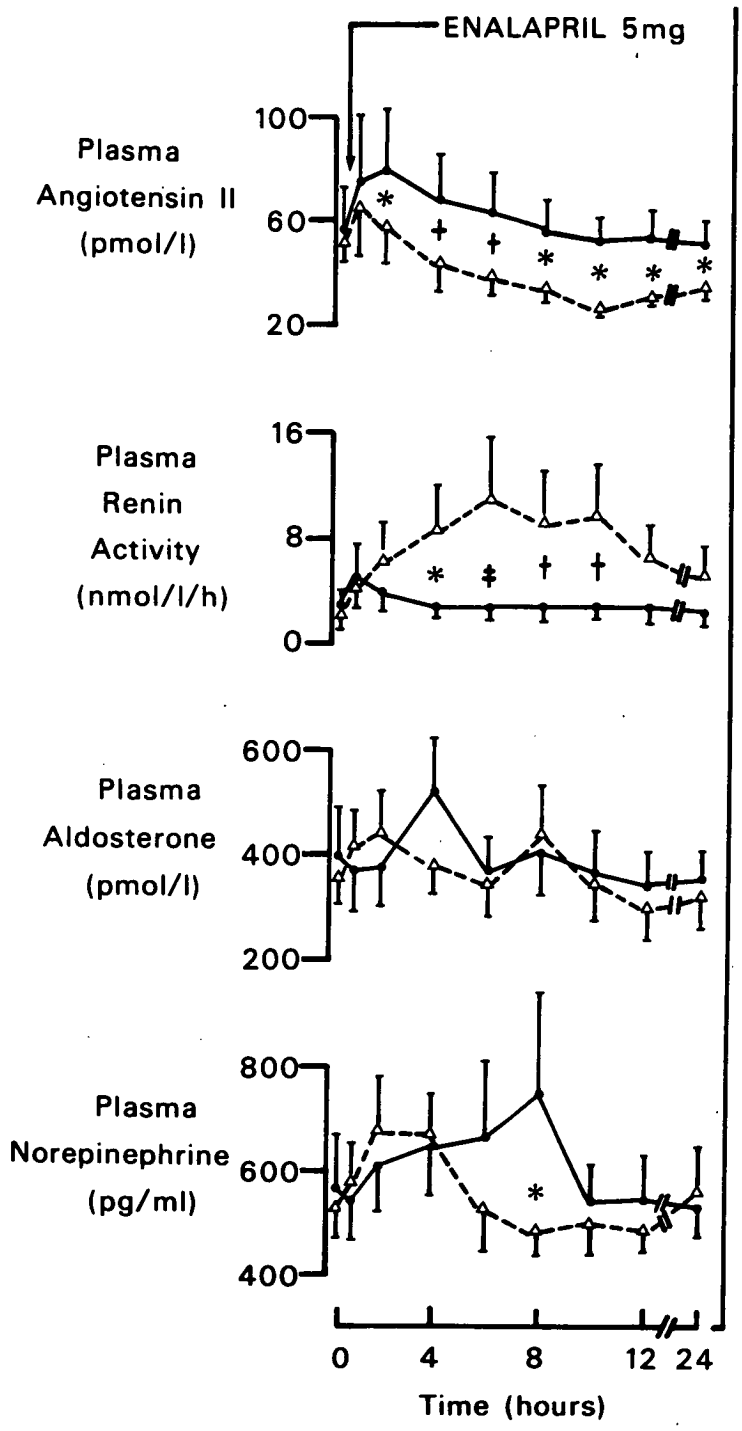
Plasma ADH levels measured at 1130 hr on the two control days varied between 0.7 and 15.2 pmol/l, which is similar to the range (0.8 to 14.3 pmol/l) observed in normal laboratory volunteers (Saddler et al, 1983). Enalapril treatment was associated with an overall decline in plasma ADH levels (see fig 6.12). Although both ADH and angiotensin II levels fell during the study, there was no relationship between them for the group as a whole ($r = -0.03$, $n = 32$), whilst in individual patients the correlations were variably positive or negative. There was, however, a positive and statistically significant association between concurrent ADH and plasma sodium concentrations ($r = 0.45$, $n = 37$, $p<0.02$).

FIGURE 6.4: DOSE RESPONSE STUDY IN PATIENT 1:



This graph compares the peak effects on plasma renin activity and mean arterial pressure following administration of incremental doses of enalapril (1.25, 2.5, 5, and 20 mg) to patient 1. Recordings made at 1530 hr each day are subtracted from the mean 1530 hr value for the two control days.

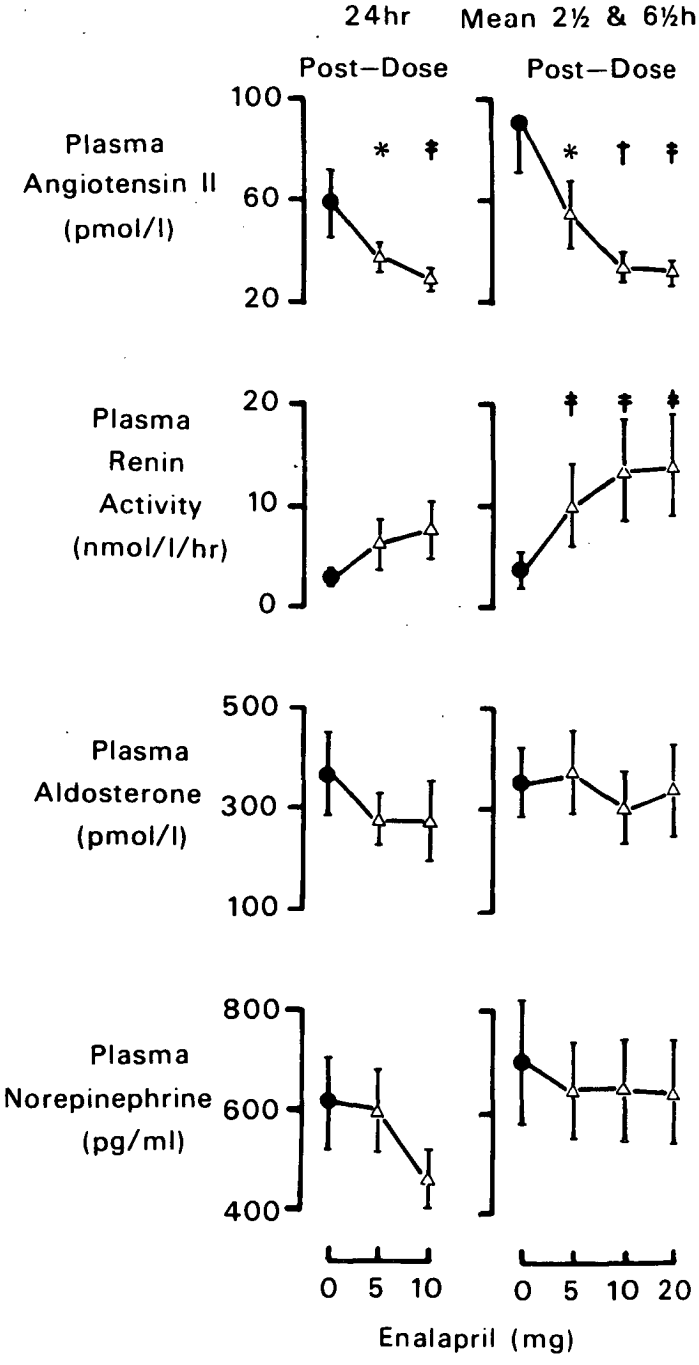
FIG 6.5: HORMONE RESPONSE TO FIRST DOSE OF ENALAPRIL:



Plasma hormone levels (mean ± SEM) in eight patients with heart failure on the control day (closed symbols) and after 5 mg of enalapril (open symbols) which was administered at 0900 hr after 0830 recordings on the second day.

* $p<0.05$, † $p<0.01$, ‡ $p<0.005$.

FIG 6.6: HORMONAL RESPONSE TO INCREMENTAL DOSES OF ENALAPRIL:



Hormone responses to daily increases in enalapril dose in seven patients with heart failure (mean ± SEM). Values at 2.5 and 6.5 hrs after enalapril (open symbols) are combined and compared with time-matched levels from two control days (closed symbols)on the right half of the figure. On the left, results 24 hrs after enalapril (0830 hr) are compared with time matched data on two control days.

* $p<0.05$, † $p<0.01$, ‡ $p<0.005$.

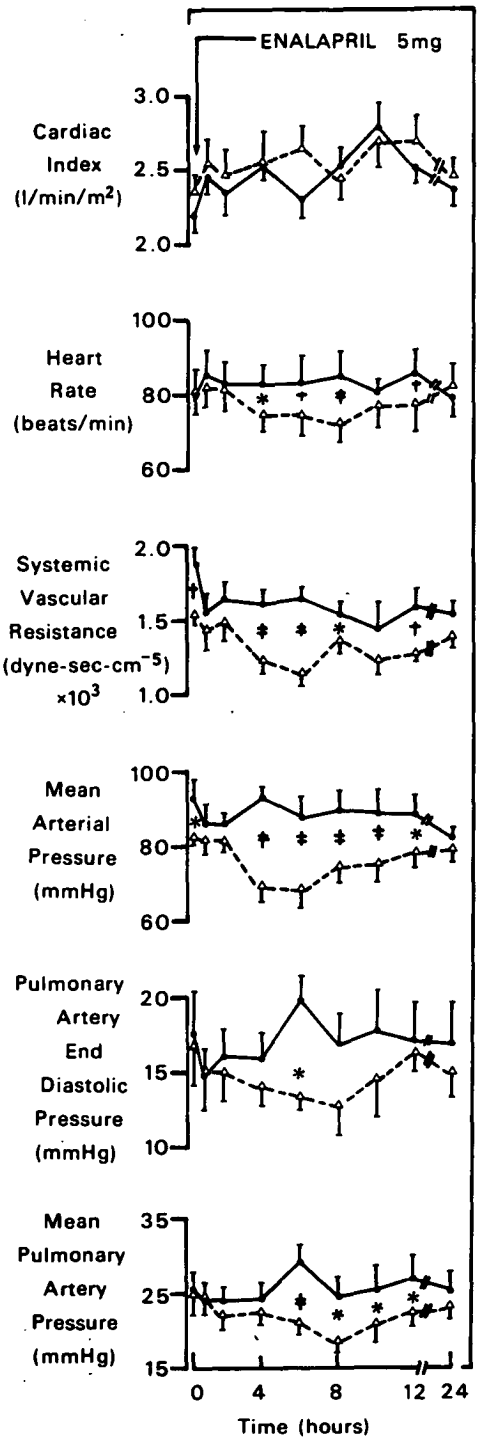
4. Haemodynamic Response:

Cardiac index was not altered significantly by the first dose of enalapril, but heart rate declined (fig 6.7) with a consequent rise in stroke index. Systemic vascular resistance and mean arterial pressure were significantly reduced after four hours and remained below control-day values until the eighth to twelfth hour (fig 6.7). Pulmonary artery end-diastolic pressure and mean pulmonary artery pressure also fell, the peak effect occurring at six to eight hours. All haemodynamic indices had returned to control-day values 24 hours after the first dose of enalapril (fig 6.7).

Results of hourly mean values for arterial pressure and heart rate recorded in three patients on the second control day and for 24 hours after enalapril administration are shown in fig 6.8. Both parameters were similar in the first two hours of each day, confirming steady state conditions. The decline in arterial pressure and heart rate was not obvious until the fourth hour after administration of enalapril. The greatest differences between the two days were 26 mm Hg for systolic pressure and 21 mm Hg for diastolic pressure recorded during the seventh hour post enalapril, while heart rate was 8 to 11 beats/minute slower. From the fifteenth hour, heart rate on the two days was indistinguishable from control levels, while arterial pressure remained lower, but within 5 mm Hg of control day levels.

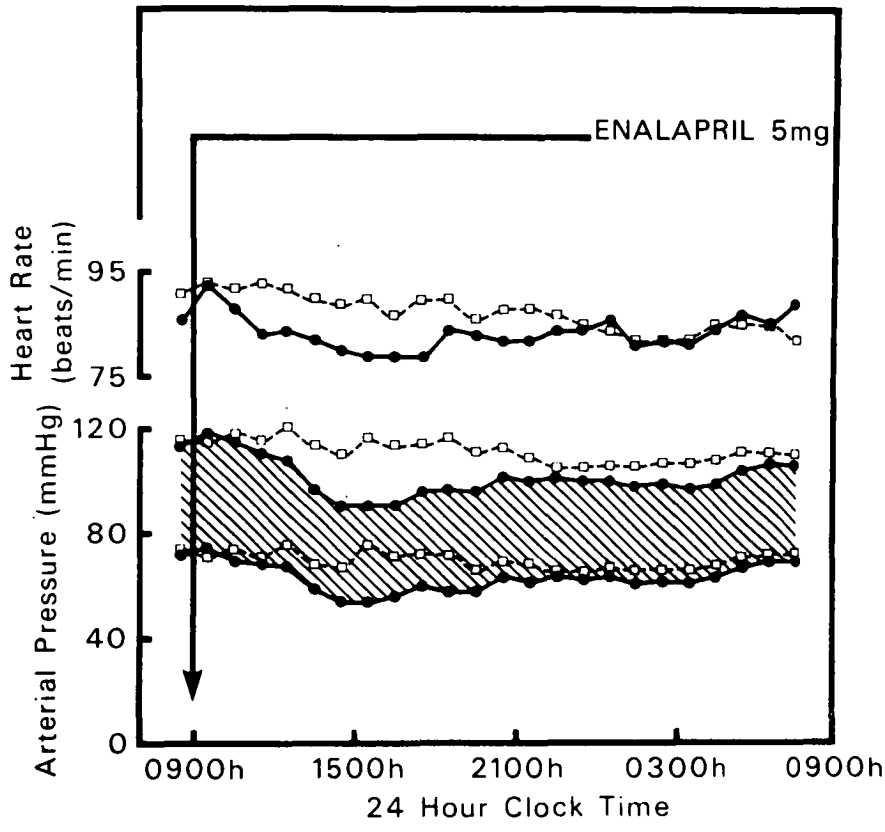
Analysis of incremental dose data showed that cardiac index and stroke index increased in a dose-related fashion when results 2.5 and 6.5 hours after the drug were combined, although this pattern was less obvious 24 hours after the drug (fig 6.9). Heart rate, mean arterial pressure, systemic vascular resistance and right heart pressure showed clear-cut decrements 2.5 to 6.5 hours after enalapril, but again the effects were less evident at 24 hours. Forearm plethysmography (fig 6.10) demonstrated no significant rise in forearm arterial blood flow, although maximum venous flow increased slightly.

FIG 6.7: HAEMODYNAMIC RESPONSE TO FIRST DOSE OF ENALAPRIL:



Haemodynamic indices (mean ± SEM) on a control day (closed symbols) and the following day after 5mg enalapril (open symbols) in eight patients with heart failure. After baseline recordings at 0830 hr enalapril was given at 0900 hr.

FIG 6.8: CONTINUOUS RECORDING OF ARTERIAL PRESSURE AND HEART RATE:



Hourly integrated mean heart rate and arterial pressure on a "control" day (open symbols), and after a single oral dose of enalapril (closed symbols). Each point represents the mean of three patients.

Legend for fig 6.9

Haemodynamic responses to increasing doses of enalapril in seven patients with heart failure (mean ± SEM). Results obtained 2.5 and 6.5 hr after enalapril (open symbols) are combined and compared with time-matched levels from two control days (closed symbols) on the right half of the figure. On the left, results 24 hours after enalapril (0830 hr) are compared with time-matched values on two control days (closed symbols).

*$p<0.05$, † $p<0.01$, ‡ $p<0.005$.

PAP denotes mean pulmonary arterial pressure.

PAEDP denotes pulmonary artery end-diastolic pressure.

SVR denotes systemic vascular resistance.

FIG 6.9: HAEMODYNAMIC RESPONSE TO INCREMENTAL DOSES OF ENALAPRIL.

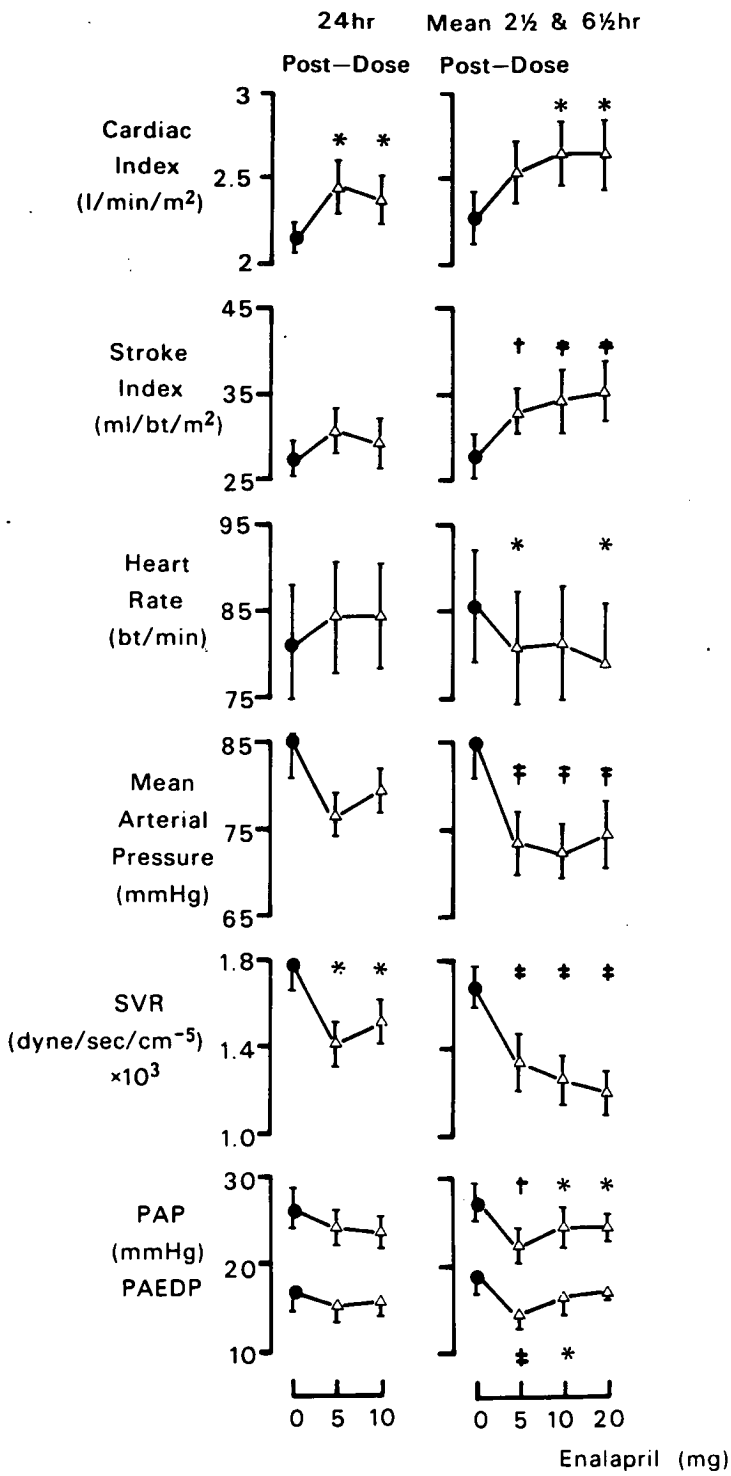
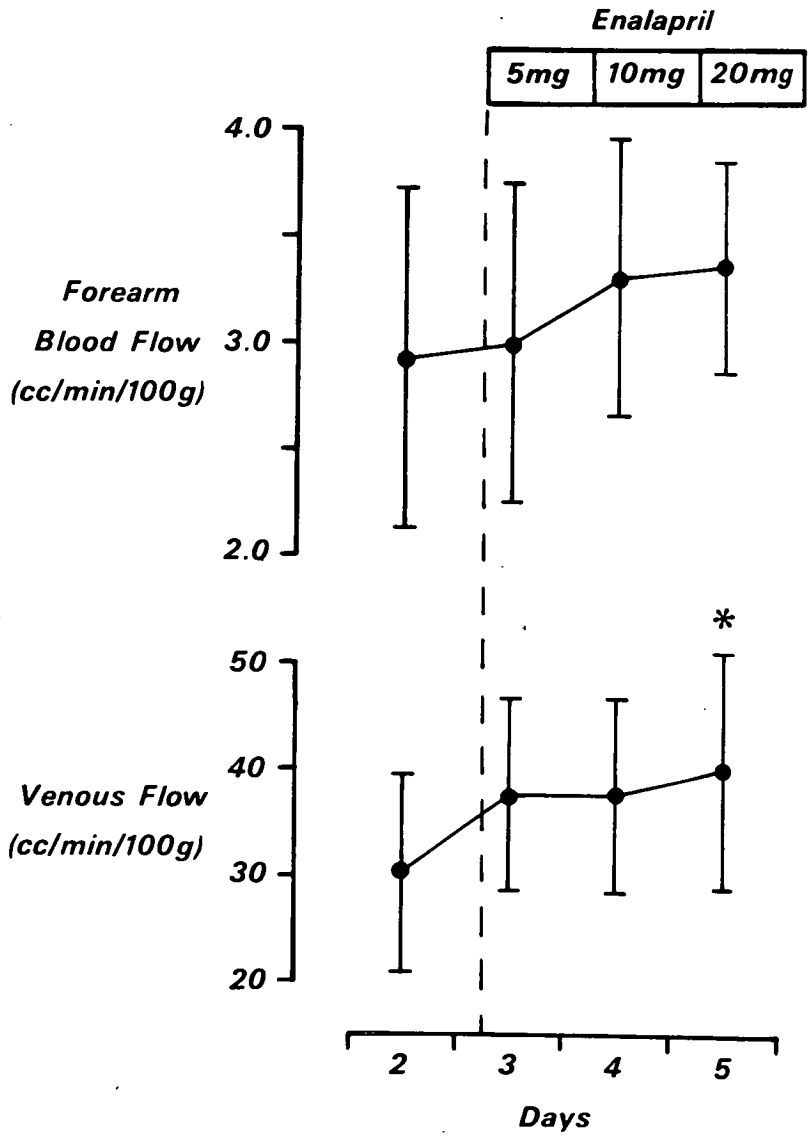


FIG 6.10: FOREARM BLOOD FLOW:



The effects of incremental doses of enalapril on forearm plethysmography performed 3.5 hours after each dose compared to measurements performed on the two control days (mean $\pm$ SEM; * $p<0.05$).

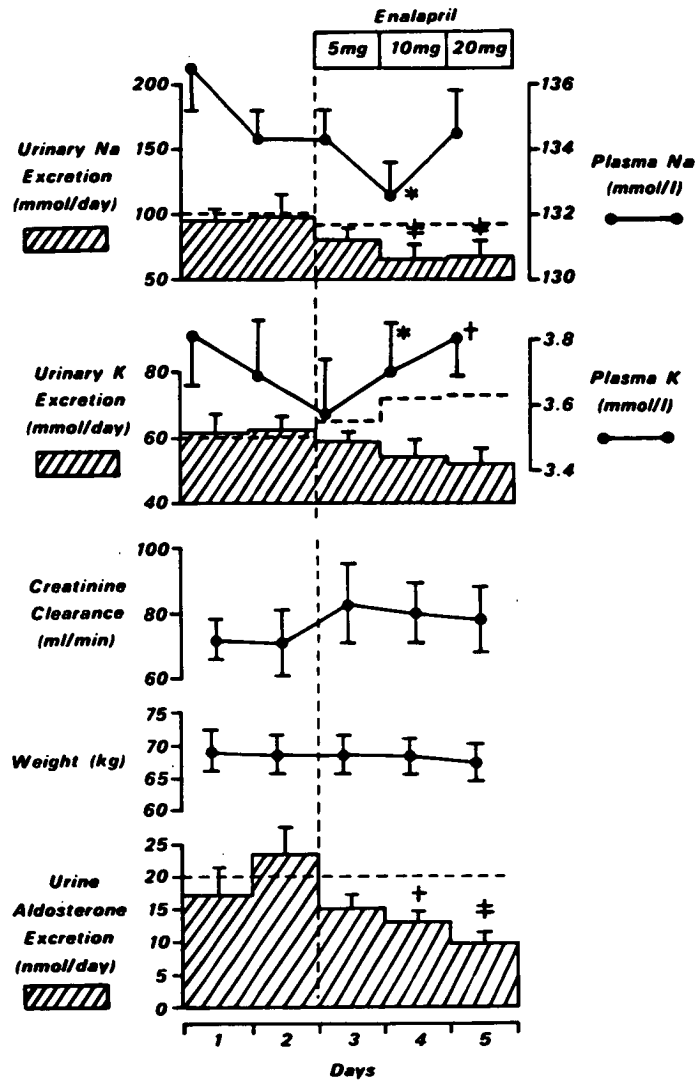
5. Relationships between hormone and haemodynamic responses:

The degree of activation of the renin-angiotensin system and the sympathetic nervous system on control days predicted haemodynamic responses to the first dose of enalapril. Thus, baseline levels of angiotensin II (mean of 0830 hr measurements on days 2 and 3) correlated with maximum increases in stroke index ($r=0.73$) and decreases in systemic vascular resistance ($r=-0.83$), pulmonary artery end-diastolic pressure ($r=-0.83$), and mean pulmonary artery pressure ($r=-0.80$; $p<0.05$ to <0.001). Likewise, baseline norepinephrine levels were related to the rise in stroke index ($r=0.69$) and the fall in pulmonary artery end-diastolic pressure ($r=-0.80$) and mean pulmonary artery pressure ($r=-0.78$; $p<0.05$ to <0.01). Comparison of the magnitude of change in hormone levels with changes in haemodynamic data was compromised by the small number of patients included in the study.

6. Twenty-four hour urine and metabolic data: (fig 6.11)

Endogenous creatinine clearance tended to increase when enalapril treatment was initiated (fig 6.11), but this was not significant. Urine sodium excretion was close to intake on the control days, but declined during the three days of enalapril treatment, when cumulative balance was positive by an average of 21 mmol/day/patient. A similar trend was seen for potassium, with a positive cumulative balance averaging 15 mmol/day/patient. Plasma potassium rose from a baseline of 3.57 ± 0.17 mmol/l to 3.80 ± 0.12 mmol/l on the third day of treatment ($p<0.01$), while initial and final plasma sodium levels were similar. Weight and plasma glucose levels were unaffected. Urine aldosterone fell in a stepwise fashion from 17 ± 4 nmol/day and 23 ± 4 nmol/day (on control days 1 & 2) to 10 ± 2 nmol/day on the third day of treatment ($p<0.01$).

FIG 6.11: METABOLIC EFFECTS OF ENALAPRIL:



Metabolic effects of incremental doses of enalapril compared with the two control days. Horizontal dashed lines for plasma ADH and urine aldosterone represent the mean of the two control days and for urine sodium and potassium excretion the horizontal dashed lines represent the mean daily intake (mean $\pm$ SEM; * $p<0.05$; † $p<0.01$; ‡ $p<0.005$).

7. Follow-up data:

1. Clinical assessment:

After four to eight weeks of enalapril treatment, the NYHA functional status had improved by two classes in one patient, one class in five patients, while two remained unchanged in Class II (table 6.2). Clinical parameters of heart failure improved in all Class III and IV patients. Reintroduction of frusemide was required on clinical grounds in two of the three patients in whom it was initially withdrawn, but the dose required was reduced (table 6.2). In the group of six whose frusemide was not withdrawn, the dose at follow-up was decreased in two, increased in one and unchanged in two, while one patient was stable without frusemide (table 6.2).

2. Treadmill Exercise Performance: (table 6.2)

Overall, there was no significant improvement in exercise performance, however, patients who were originally more severely limited increased their exercise capacity, while less severely afflicted individuals showed little change or a slight deterioration (fig 6.12). Patient 4 developed intermittent calf claudication after enalapril therapy was commenced, which curtailed his exercise performance. No significant alteration in maximum heart rate, systolic blood pressure or their product was observed.

3. Radionuclide ejection fraction: (table 6.2)

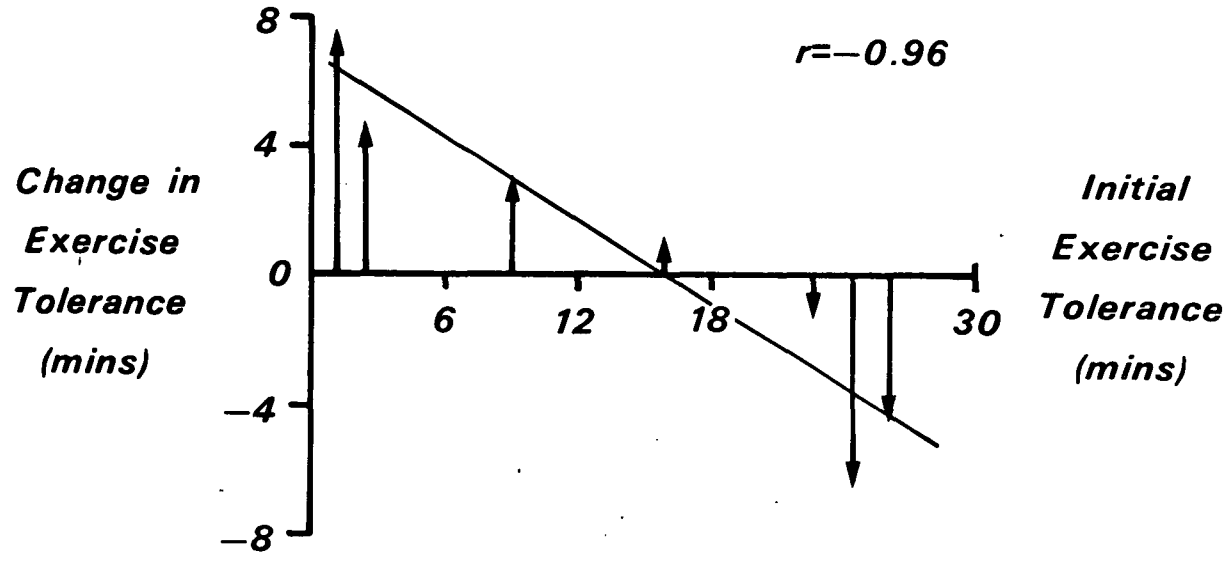
There was no overall significant improvement in ejection fraction, although it increased in six patients. The change in exercise performance correlated with the change in ejection fraction ($r = 0.81$; $p<0.05$) (fig 6.13).

TABLE 6.2: FOLLOW-UP DATA:

Patient	NYHA Class		Radionuclide LVEF(%)		Exercise Capacity(mins)		Frusemide (mg/day)		Enalapril Dose
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	(mg/day)
1	II	II	25	23	-	-	40†	0	
2	III	II	31	39	16.5	17.5	160†	40	10
3	II	II	-	-	9.0	12.0	40†	20	20
4*	II	II	11	12	26.0	21.7	40	0	20
5	III	II	13	15	-	-	80	20	20
6‡	IV	III	24	28	2.5	6.8	250	500	10
7‡	III	II	26	36	22.3	21.5	250	250	20
8	III	II	8	6	24.5	18.1	500	500	10
9‡	IV	II	15	30	0.9	8.3	250	120	10
Mean	3.0	2.1	19.1	23.6	14.5	15.1	179	161	
SEM			3.2	4.5	4.3	2.6	53	73	
P	<0.05		0.05<p<0.1		NS		NS		

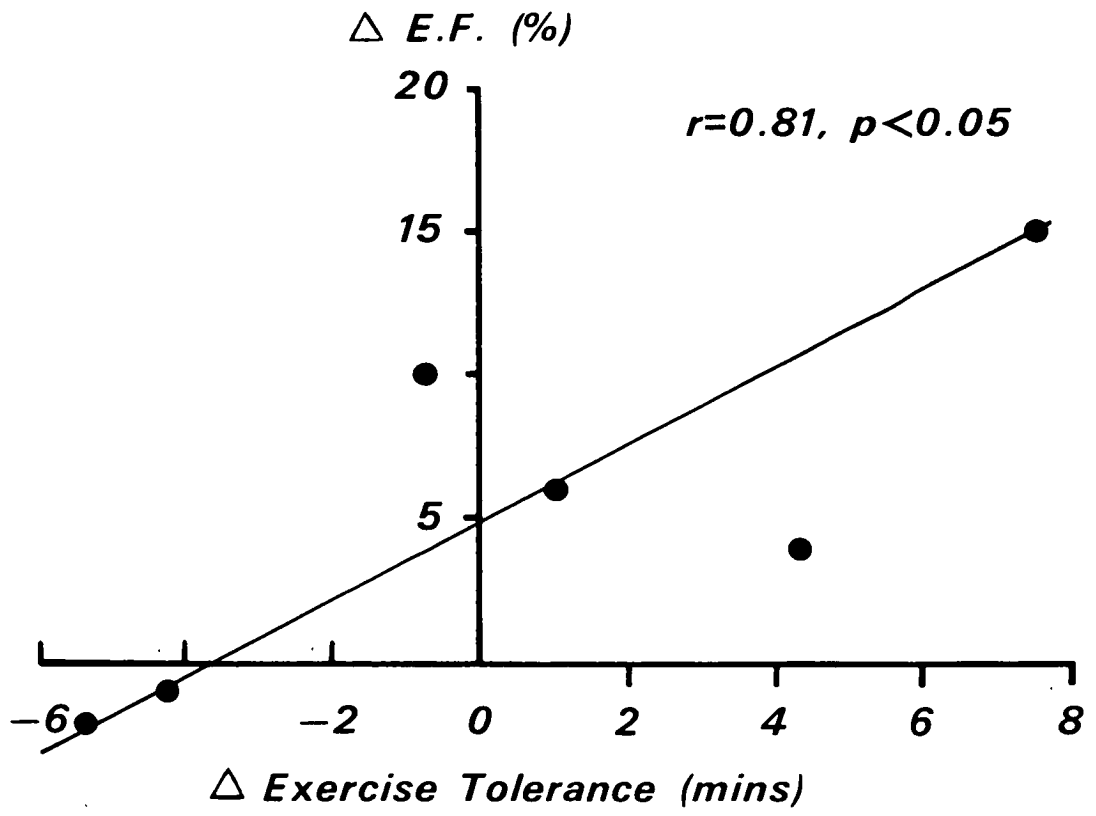
Results are shown before enalapril (Pre), and at follow-up four to eight weeks after commencing enalapril (Post). * This patient developed claudication during follow-up treadmill exercise testing. NS denotes not statistically significant. † = frusemide withdrawn four days before invasive study in these patients. ‡ = LVEF determined "Nuclear Stethoscope".

FIG 6.12:



Effect of enalapril on exercise tolerance, compared with pre-treatment exercise tolerance.

FIG 6.13:



Relationships between change of ejection fraction and exercise capacity produced by enalapril in six patients.

4. Side effects:

No serious side effects occurred during the trial period, but one patient did develop claudication during follow-up exercise testing. No patient developed abnormalities in routine blood screen, or SMAC 11 analysis, while proteinuria was not encountered.

8. Relationships between initial response and follow-up data:

Due to small numbers and biological variability, analysis can at best be descriptive. The patients could be subdivided into two distinct groups according to prior activation of the renin-angiotensin-aldosterone system:

A. Initial plasma renin activity < 1 nmol/l/hr;
and B. Initial plasma renin activity > 1 nmol/l/hr.

Patients in the second group, not surprisingly, had higher initial plasma levels of angiotensin II, urine aldosterone excretion, pulmonary artery end-diastolic pressure, systemic vascular resistance and frusemide dose. They were also more severely impaired according to NYHA Functional Class.

Enalapril produced a greater rise in plasma renin in group B, while plasma angiotensin II and urinary aldosterone excretion fell to a greater extent. This was associated with a better haemodynamic response, greater improvement in functional state and exercise capacity in two patients. On the other hand, the dose of frusemide could be reduced more readily in group A patients following completion of the study.

6.5 DISCUSSION:

Angiotensin converting enzyme inhibition has brought a new dimension to the management of cardiac failure. Captopril, the only currently available oral converting enzyme inhibitor has proved most effective in patients who are resistant to conventional therapy (Maslowski et al, 1981a; Dzau et al, 1982). Although side effects are not common with captopril, potentially serious complications have been reported (Vidt et al, 1982). Enalapril (MK-421), a member of a new group of converting enzyme inhibitors which lacks a mercapto function and is characterised by weak chelating properties, has recently been synthesized (Patchett et al, 1980) and used successfully in hypertension (Gavras et al, 1981). Preliminary data suggest it is as effective and longer acting than captopril in hypertension, and so far serious side effects have not been observed. In this study the hormonal, haemodynamic and electrolyte response to enalapril in patients with cardiac failure are documented.

A dose finding study was performed in patient 1. Doses of 2.5 and 5 mg produced moderate rises in plasma renin activity and fall in mean arterial pressure. As preliminary studies in hypertension suggested that a starting dose of 5 mg was effective (Gavras et al, 1981), this dose was chosen for the present study.

The data show that enalapril induces clearcut changes in angiotensin II, plasma renin activity and urine aldosterone excretion. Whilst plasma angiotensin II and urine aldosterone excretion declined, there was a reciprocal rise in plasma renin activity resulting from loss of tonic inhibition of secretion by angiotensin II. These effects are similar to those reported with captopril (Maslowski et al, 1981a; Dzau et al, 1980). However, onset of action and the nadir were delayed compared to captopril (Ader et al, 1980), and the decline in plasma angiotensin II was sustained for 24 hours after a 5mg dose - in contrast to the shorter duration of action of captopril in heart failure (Nicholls et al, 1982). This observation raises the possibility that enalapril might be effective when administered once or at most, twice daily. For some indices, the magnitude of change was greater with 10

and 20 mg of enalapril than with 5 mg, suggesting that the larger doses may be optimal.

It may appear surprising that plasma aldosterone levels did not fall after the first dose of enalapril, especially since our group reported the dominant role of angiotensin II in regulating aldosterone in heart failure (Nicholls et al, 1981). However, baseline levels of plasma aldosterone were not elevated in most of our patients, in contrast to those studied prior to the initiation of captopril treatment (Maslowski et al, 1981a). The dependence of aldosterone secretion on angiotensin II presumably relates to the degree of activation of the renin-angiotensin-aldosterone system. Where this is relatively minor, as in the present study, blockade of angiotensin II formation might not necessarily result in an acute decline in aldosterone. Nevertheless, aldosterone excretion fell during the three days of incremental enalapril treatment, and a similar (though less impressive) decline in plasma aldosterone was observed. In this study, aldosterone secretion was regulated in part by angiotensin II, but the primacy of the renin-angiotensin system was less obvious than in patients with extreme activation of this system.

Plasma ADH levels prior to enalapril were within our normal range for healthy ambulatory volunteers, but decreased gradually during the five day study. The regulation of circulating ADH is multifactorial and complex (Robertson, 1977). Although the fall in angiotensin II levels may have contributed to the observed change (Sladek & Joynt, 1979), the lack of statistical correlation either in individuals or in the group as a whole tends to mitigate against a cause and effect relationship. Instead of a fall in ADH secretion, it is possible that its clearance rate increased. ADH is predominantly cleared by kidney and liver (Janacky et al, 1982), thus improved flow to these organs could well have increased clearance from plasma.

The results from this study show objective haemodynamic improvement during acute enalapril therapy. The elevated systemic vascular resistance was reduced as a consequence of the decline in circulating angiotensin II, and perhaps also in part to sympathetic withdrawal as

indicated by the fall in circulating norepinephrine levels and reduction in heart rate. Unmeasured factors such as bradykinin and prostaglandins may also have contributed to the pattern of observed haemodynamic changes. Cardiac index increased during the study, while right heart pressures declined, presumably as a result of improved left ventricular performance but perhaps due in part to a decline in cardiac pre-load.

The nadir of the haemodynamic response occurred approximately six to eight hours after the first dose and corresponded to the nadir of hormone changes. The smooth temporal profile may be of practical importance where a sudden fall in arterial pressure produced by drugs with a faster onset of action (eg captopril) could be hazardous, especially in patients with a compromised cerebral or coronary circulation (Baker et al, 1980). Despite significantly lower levels of plasma angiotensin II 24 hours after the first dose of enalapril, haemodynamic indices were not significantly different from baseline recordings. Continuous monitoring in three patients (fig 6.8) showed that arterial pressure was lower at 24 hours but the differences were much less than at peak effect. Greater cumulative effect 24 hours after a further 10 mg dose of enalapril showed lower plasma angiotensin II levels and systemic vascular resistance, while cardiac index was higher (fig 6.6 and 6.9), suggesting that the duration of effect of the drug is greater than 24 hours.

The multiple factors responsible for the excessive vasoconstriction characteristic of chronic congestive heart failure include enhanced sympathetic nervous activity, activation of the renin-angiotensin system and disturbed reactivity of the vessel wall (Zelis et al, 1979). The vasoconstriction of chronic heart failure occurs differentially in the various regional circulatory beds (Mason et al, 1970). Limb plethysmography has failed to show vasodilatation of arteries or veins with teprotide (Faxon et al, 1980). Captopril did not affect muscle blood flow, but increased limb venous capacitance indirectly, presumably as a result of reduced sympathetic tone (Faxon et al, 1981). It appears from this study, that enalapril also has little effect on resting limb flow in heart failure. The enhanced cardiac output must be selectively re-distributed to other regional beds, but, this does not imply that

muscle perfusion during exercise is not improved.

The most striking haemodynamic improvement was observed in subjects in whom activation of the renin-angiotensin-aldosterone system and sympathetic nervous system was most intense. These patients were on higher doses of frusemide and were subjectively and objectively more severely impaired. Moreover, these patients had the greatest improvement of symptoms and exercise capacity on enalapril. While patients with less activation of the renin-angiotensin-aldosterone system had a less marked hormonal, haemodynamic and exercise response, the dose of diuretics could be reduced without complication on completion of the follow-up protocol. Enalapril diminished the exercise capacity in some patients who were initially only mildly impaired. This may, in part, be due to withdrawal or reduction in diuretic therapy. One patient developed claudication on enalapril, presumably due to reduced blood flow resulting from a reduced perfusion pressure across fixed stenoses of lower limb arteries. Such ischaemic events appear to occur rarely with converting enzyme inhibitors (Romankiewicz et al, 1983). No other serious side-effects were observed.

As with captopril (Maslowski et al, 1981a), a positive cumulative potassium balance and a rise in plasma potassium were seen, and presumably resulted from reduced aldosterone effect. Thus plasma potassium needs to be monitored when enalapril treatment is initiated. During the first three days of enalapril treatment, a positive cumulative sodium balance was also observed. This appears to be of little consequence in the longer term since frusemide requirements were reduced or unchanged in all but one patient after four to eight weeks of treatment.

Divergent findings and considerable inter individual variation in the effects of captopril on renal blood flow and indices of renal function have been observed in heart failure patients. Within one to two hours of acute captopril administration (50 to 100 mg), mean arterial pressure declined, while renal blood flow increased 50 to 60% but glomerular filtration rate remained constant (Creager et al, 1981). These changes were associated with a two-fold increase in urinary sodium

excretion and potassium retention. In contrast, completely opposite acute effects were observed by Mujais et al (1981), but all parameters returned to baseline values after two days of captopril therapy. Pierpoint et al (1981) demonstrated similar detrimental effects on renal function after three days of captopril therapy and showed an inverse relationship between the change in blood pressure and changes in sodium excretion suggesting that acute effects were due to reduced perfusion pressure. Our data on the use of enalapril is compatible with the latter view although we did not assess the effect on renal haemodynamics. On the other hand, these acute effects appear to be of little long term consequence since frusemide requirements were reduced or unchanged in all but one patient after four to eight weeks of treatment. However, it should be noted that Dicarlo et al (1982) have recently found that an increase in diuretic therapy was required following long term therapy with enalapril. The long term effects of enalapril on renal function will thus require further investigation.

6.6 CONCLUSION:

Enalapril is a long-acting converting enzyme inhibitor which induces clear-cut haemodynamic improvement in patients with heart failure. Because of its long duration of action and delayed onset, hypotension is more gradual in onset than the only currently available converting enzyme inhibitor, captopril. This should reduce acute ischaemic complications that occur occasionally with captopril. The drug will probably be effective when given once or at most twice daily, thus it will probably replace captopril, especially as there appear to be less side-effects with enalapril.

The magnitude of haemodynamic improvement is related closely to pre-treatment activity of the renin-angiotensin-aldosterone system and sympathetic nervous system. Chronic therapy is well tolerated with no major side-effects apart from the development of calf claudication in one patient. Clinical condition improved in most patients while exercise performance improved in those patients who were initially severely afflicted. Short-term studies such as this one, however, do not allow extrapolation to long-term effects or changes in mortality. Such studies are warranted.

CHAPTER 7

HAEMODYNAMIC, HORMONAL AND ELECTROLYTE EFFECTS OF PRENALTEROL INFUSION IN HEART FAILURE :

7.1 INTRODUCTION:

It would be rational to concentrate therapeutic endeavours on the primary pathophysiological abnormality in cardiac failure - diminished myocardial contractility. However, there has been no major advance in chronic inotropic treatment for heart failure since the introduction of digitalis, and even now the place of this agent for patients in sinus rhythm remains uncertain (Selzer, 1981). Several potentially useful agents have been investigated (Slutsky 1981, Lejemetel et al 1979, Dawson et al 1981).

Reports that a selective beta-1 agonist, prenalterol, improves myocardial function in patients with heart failure are encouraging, especially as the drug may be effective when given by mouth (Waagstein et al, 1979). At present, available data relate largely to its administration over a period of minutes only and there is a dearth of dose/response information. Moreover, the effects of the drug on neurohumoral systems and electrolytes have received scant attention. The present study documents haemodynamic, hormonal and electrolyte changes during three days of an incremental prenalterol infusion in six patients with cardiac failure.

Before describing the study in detail, it is pertinent to briefly review the place of inotropic therapy in chronic heart failure.

7.2 THE ROLE OF INOTROPIC THERAPY IN CHRONIC HEART FAILURE:

As I outlined in Chapter 1, the aim of treatment of chronic cardiac failure is to correct and reverse the pathological sequence that led to the development of the clinical syndrome. This entails:

1. Improving myocardial contractility;
2. Reducing the workload of the heart by restriction of physical activity and vasodilators;
3. Reducing salt and water retention.

At the turn of the century, there was great enthusiasm for finding effective inotropic agents (Coupland 1897, Yoo 1906). Today the search continues. Digitalis is the only inotropic agent currently recognised as effective in the long-term management of chronic heart failure. Even now, the place of this agent for patients in sinus rhythm remains uncertain (Selzer, 1981). Symptoms of cardiac failure often persist despite digitalis and diuretic therapy. Consequently, the pharmaceutical industry has invested considerable effort in developing new inotropic agents (Table 7.1). Some potent cardiotonic agents such as dobutamine, dopamine and amrinone will augment cardiac performance in patients refractory to standard treatment (Leier et al, 1977; Benotti et al, 1978), thus they may improve the outlook of such patients.

Inotropic agents act directly on the failing myocardium to augment its contractile state and improve pump function (Weber, 1982a). Systemic blood flow is augmented and apportioned to each organ according to the autoregulatory behaviour of its vascular bed. Thus, oxygen delivery to the metabolising tissues is enhanced while ventricular filling pressure and organ congestion decline.

At the cellular level, contractility is governed by the quantity of calcium ion released at the actomyosin junction (Fabiato A & S, 1977). Inotropic agents with a recognised mechanism of action augment myocardial contractility by increasing the amount of calcium ion available to the contractile proteins. Cardiac glycosides inhibit the sodium pump of the sarcolemma, thereby allowing intracellular accumulation of sodium which displaces bound calcium ions (Opie, 1980).

Sympathomimetic agents (Table 7.1) bind reversibly to beta-adrenergic receptors on the cardiac cell surface, activate adenyl cyclase thereby raising intracellular cyclic AMP production. Glucagon and xanthines have the capacity to increase intra-cellular cyclic AMP without involving the beta-receptor. The elevation of the intracellular concentration of cyclic AMP may increase the number of active or open sarcolemmal calcium ion channels, thereby increasing the intra-cellular concentration of this ion (Weber, 1982a). The mechanism by which the bipyridine derivative amrinone augments myocardial contractile state remains unknown (Aloussi et al, 1979).

Investigations of the role of these new inotropic agents in chronic heart failure, however, are preliminary at present. Some major questions remain to be answered:

1. Is the inotropic effect sustained in the long-term?

2. Will the chronic increment in contractility prove harmful to the failing heart by increasing the oxygen requirements of the myocardium?

3. Sympathomimetic agents often precipitate ventricular arrhythmias in low output syndromes due to myocardial infarction (Opie, 1980). Will they do the same in heart failure?

4. What are the effects of these agents on neurohumoral systems, suspected to play a part in the development of tolerance to other forms of therapy?

These questions, with particular reference to prenalterol, will be addressed in the discussion to the following investigation.

TABLE 7.1 INOTROPIC AGENTS AND THEIR MODE OF ACTION:

1.	Calcium	
2.	Digitalis Glycosides	Na-K ATPase inhibition
3.	Sympathomimetics:	
	a. Intravenous	
	Norepinephrine	B_1 stimulation increases intracellular Cyclic AMP
	Isoprenaline	
	Epinephrine	
	Dopamine	
	Dobutamine	
	b. Oral	
	Prenalterol	B_1 stimulation
	Butopamine	
	Pirbuterol	B_2 & (?) B_1 stimulation
	Salbutamol	
4.	Xanthines (eg theophylline)	Phosphodiesterase inhibition increases cyclic AMP
5.	Glucagon	Increases cyclic AMP
6.	Amrinone	?

7.2 METHODS :

1. Patients and study protocol:

The protocol was approved by the hospital's Ethical Committee, and all patients gave informed written consent.

Clinical details of the six patients are summarized in Table 7.2. All had suffered at least one episode of pulmonary oedema, but had responded to routine treatment. At the time of entrance to the study, their therapy (Table 7.2) had remained unchanged for at least three months. Patient 1 was also being treated with perhexilene and disopyramide which were withdrawn one week prior to the study.

TABLE 7.2: PRETREATMENT PATIENT CHARACTERISTICS:

Patient	Age (yr)	Sex	NYHA Class	LVEF *	Aetiology	Drug therapy (mg/day)
1	60	M	III	14%	IHD	D(0.25),F(120),P(2)
2	54	M	II	22%	DCM	D(0.25),F(80)
3	53	M	II	28%	DCM	D(0.25),F(120),HD(50)
4	58	M	II	13%	DCM	D(0.5),F(80),P(10)
5	60	M	III	23%	IHD	D(0.25),F(200),P(20),T(100)
6	46	M	II	17%	DCM	D(0.25),F(40),HD(100)

* = measured by single plane angiography

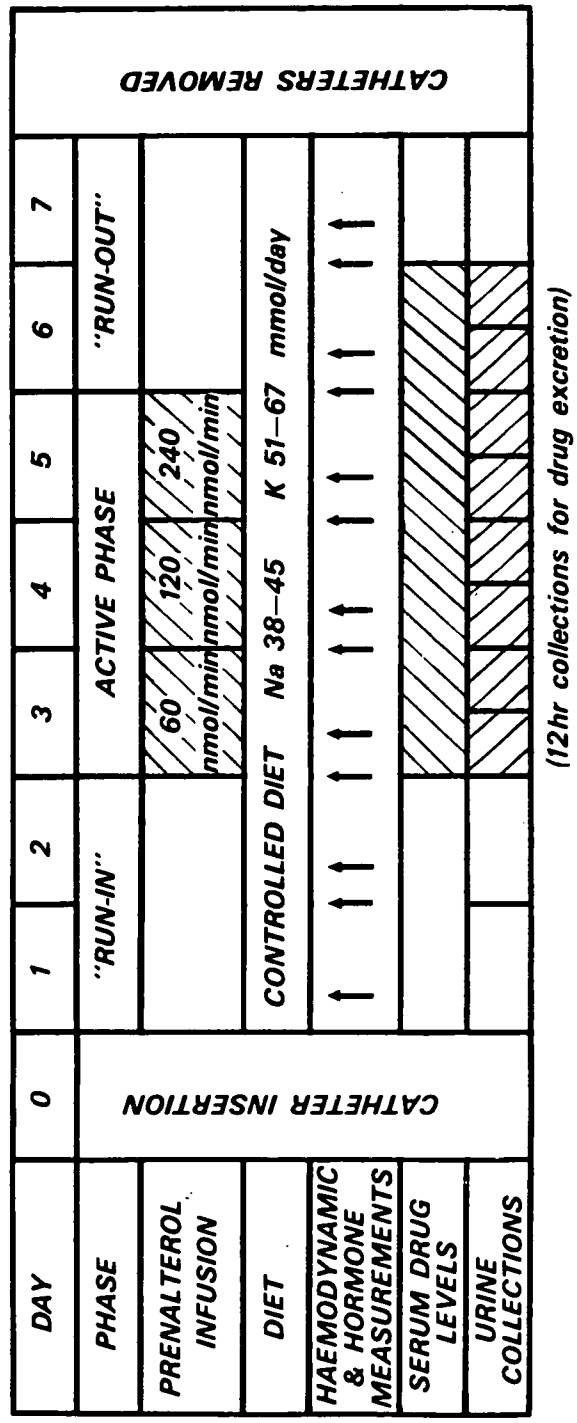
DCM = dilated cardiomyopathy
IHD = ischaemic heart disease

D = digoxin F = frusemide
P = prazosin HD = hydrallazine
T = triamterene

Legend for Figure 7.1:

Catheters were inserted at 1600 hr on the day prior to commencing the study, which entailed a two day "run-in" period, followed by three days of incremental infusion of prenalterol, then a two day "run-out" period. Haemodynamic and hormonal measurements were made twice daily at 0830 and 1530 hrs. Dietary sodium and potassium were held constant throughout. Daily collections of urine were stored on ice for electrolyte and hormone excretion.

FIGURE 7.1: STUDY PROTOCOL



2. Study Protocol:

The seven day protocol, summarised in fig 7.1, entailed a two day "run-in" period, three days of incremental prenalterol infusion, and two "run-out" days after the termination of prenalterol therapy. Throughout the seven days each patient received a diet of constant sodium (38 - 45 mmol/day), potassium (51 - 67 mmol/day), and carbohydrate content. All urine obtained by means of an indwelling bladder catheter, was retained as 24 hour collections on ice for electrolyte and hormone analysis. The patients remained semi-supine throughout. Blood sampling for hormone and electrolyte measurements, and haemodynamic recordings were carried out twice daily at 0830 hours (fasting) and 1530 hours. Digoxin and diuretics were administered immediately after the 0830 hr recordings, whilst vasodilator therapy was given after the 0830 hr and 1530 hr recordings. The dose of these medications remained constant for each patient.

3. Prenalterol Administration:

The drug was diluted in a 5% dextrose-in-water solution, and infused intravenously in an incremental fashion at 60,120 and 240 nmol/minute, each rate for 24 hours, beginning at 0900 hr. The dextrose solution was administered at 10 ml/hr throughout using an IVAC pump. During "run-in" and "run-out" days, 5% dextrose was infused at the same rate (10 ml/hr) through the right atrial port of the Swan-Ganz catheter. Patient 6 developed acute gout, consequently the protocol in this case was shortened to two days of prenalterol infusion at 60 and 120 nmol/min each for 24 hours followed by one "run-out" day. For technical reasons, patient 3 was only studied for one "run-out" day. As a result of these protocol deviations, the data for patient 6 are considered separately, and graphical display of the data only shows complete "run-out" data for the first day.

4. Haemodynamic Measurements:

On the morning of the first study day a triple lumen Swan-Ganz catheter was inserted (see Chapter 4) under strictly sterile conditions into the pulmonary artery for measurements of right heart pressures and cardiac output. A radial artery was cannulated for arterial pressure monitoring and for blood sampling. Haemodynamic recordings, and blood sampling for hormone analysis were performed concurrently at 0830 hr and 1530 hr daily. Forearm blood flow was measured at 1600 hr each day by plethysmography using a mercury-filled rubber strain gauge (Chapter 4).

5. Hormone and Electrolyte Measurements:

Arterial samples were drawn at 0830 hr and 1530 hr daily for the measurement of plasma renin activity, angiotensin II, aldosterone, cortisol, epinephrine and norepinephrine (see Chapter 5). Fasting plasma glucose (glucose oxidase method) was determined daily at 0830 hr, whilst fasting arterial samples were drawn for measurements of plasma insulin (Scott et al, 1980), glucagon (Aquilar-Parada et al, 1969), and pancreatic polypeptide (by radioimmunoassay using a polyethylene glycol separation technique), at 0830 hr on the second "run-in" day and again at 0830 hr at the completion of the third day of prenalterol infusion. Urine aldosterone and cortisol excretion were measured in 24 hour collections by radioimmunoassay. Sodium and potassium in plasma, urine and duplicate diets were determined by flame photometry.

6. Statistical Methods.

Repeated measures analyses of variance were carried out on all variables using programme P2V of the BMDP package. The initial hypothesis tested was that no daily variation occurred, and where variables were measured twice daily, no diurnal variation occurred. For indices exhibiting significant daily variation, further comparisons using T-tests, with appropriate mean square error terms from the analysis of variance, were performed to determine when these changes occurred. In the case of variables measured twice daily, the interaction of days and time of day was clearly non-significant, thus it was possible to compare the daily mean values for each index.

7.4 RESULTS:

1. General:

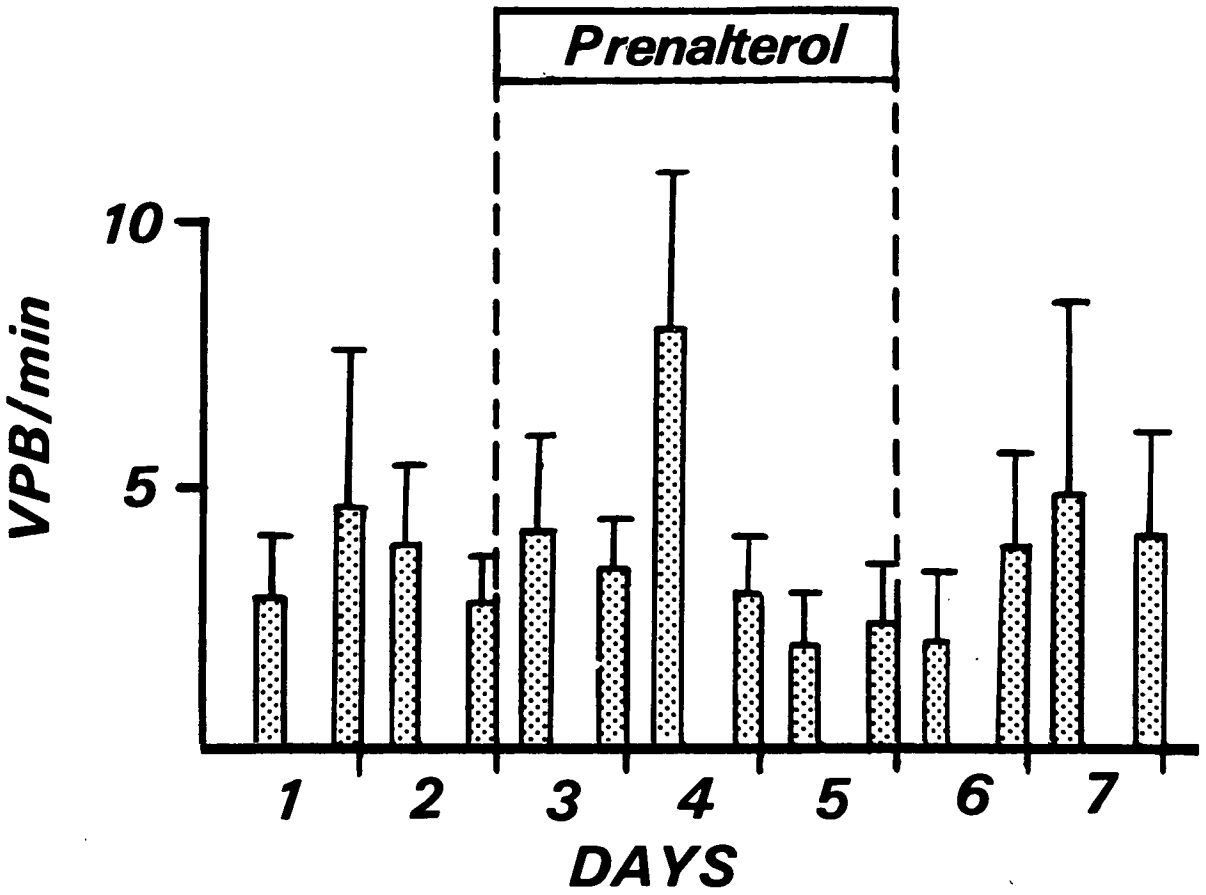
Prenalterol was well tolerated, there being no subjective changes on close questioning. No serious arrhythmias were observed during the study, and the incidence of ventricular premature beats measured at one minute intervals at 0830 hr and 1530 hr daily, was not altered by prenalterol administration (fig 7.2). As the study in patient 6 was shortened, his data are presented separately.

2. Haemodynamic responses:

Cardiac index increased from a pre-treatment mean value (± SEM) of 2.4 ± 0.2 $l/min/m^2$, to 2.7 ± 0.2, 2.8 ± 0.3, and 3.0 ± 0.3 $l/min/m^2$ on subsequent days of prenalterol infusion, then declined to a mean of 2.6 ± 0.8 $l/min/m^2$ upon cessation of the drug (fig 7.3). This represented 13%, 17% and 25% increments in cardiac index above baseline during the three days of prenalterol infusion. Stroke index changes paralleled those of cardiac index (fig 7.3). Forearm blood flow, as measured directly by strain gauge plethysmography increased in a dose-response fashion from a baseline of 2.9 ± 0.6 ml/min/100g of tissue to a maximum of 4.0 ± 0.6 ml/min/100g of tissue on the third prenalterol day, then declined when the drug was withdrawn (fig 7.3). These changes in measured forearm blood flow matched stepwise decrements in calculated systemic vascular resistance (fig 7.4). Mean pulmonary artery pressures and right atrial pressures were unchanged, but a statistically significant decline in pulmonary capillary wedge pressure was noted during the lowest rate of prenalterol infusion, and was sustained during the final two study days (fig 7.3).

Heart rate and arterial pressure showed no tendency to increase during prenalterol administration, and the product of rate and systolic pressure therefore remained stable (fig 7.4). While systemic vascular resistance declined significantly, the calculated pulmonary vascular resistance was not altered (fig 7.4).

FIGURE 7.2: EFFECT OF PRENALTEROL ON VENTRICULAR ECTOPY:

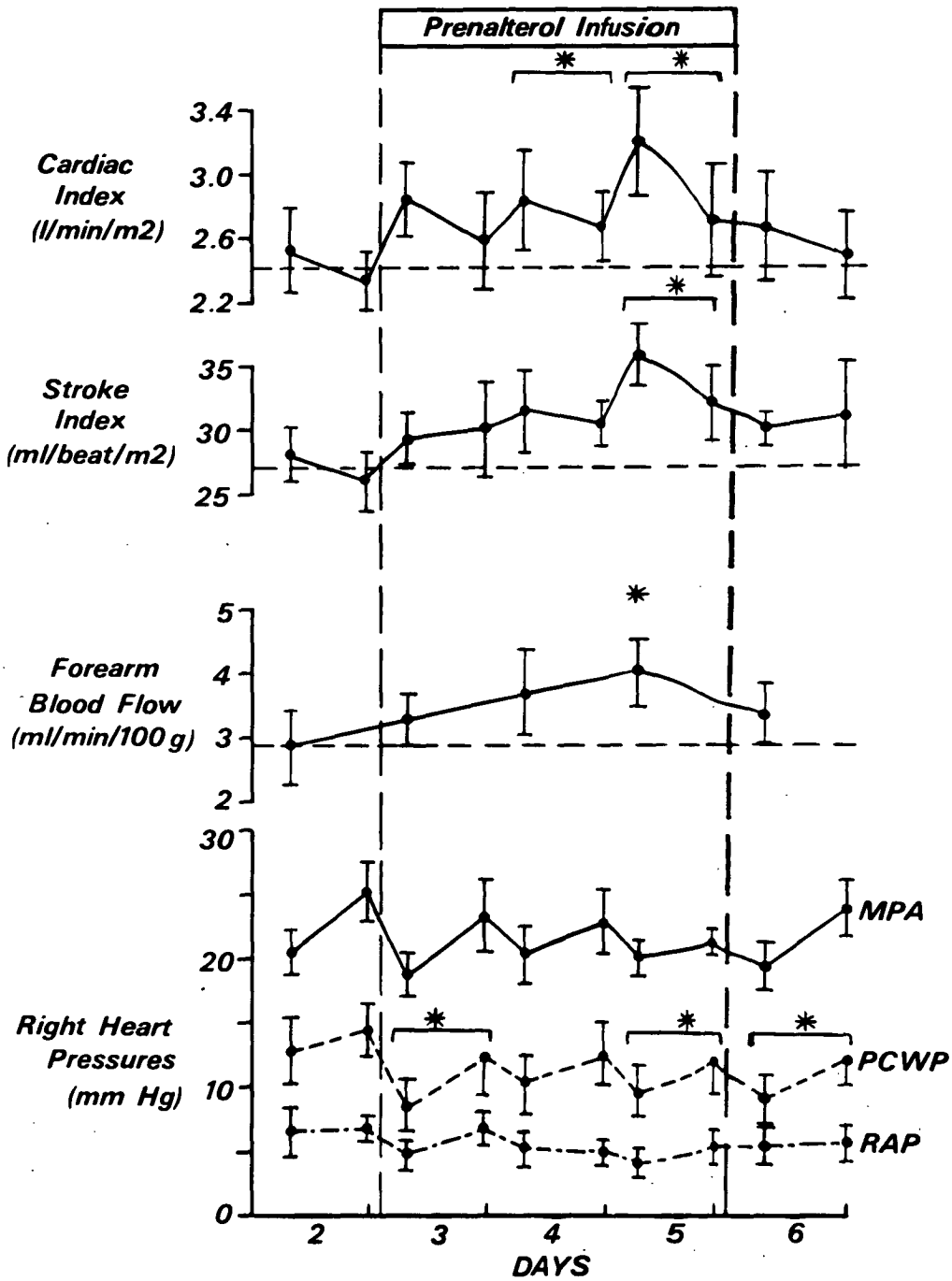


The frequency of ventricular premature beats (VPB/min) was measured over a one minute interval at 0830 and 1530 hrs daily. Results are expressed as mean ± SEM.

Legend for Figure 7.3:

Haemodynamic indices in five patients with heart failure before, during and after prenalterol infusion (mean $\pm$ SEM). Recordings were made 6.5 and 23.5 hrs after commencing each infusion rate. The discontinuous lines represent mean "run-in" levels for each index. The bars with asterisks indicate significant changes from the "run-in" values (* $p<0.05$, ** $p<0.01$). MPA = mean pulmonary artery pressure, PCWP = mean pulmonary capillary wedge pressure, and RAP = mean right atrial pressure.

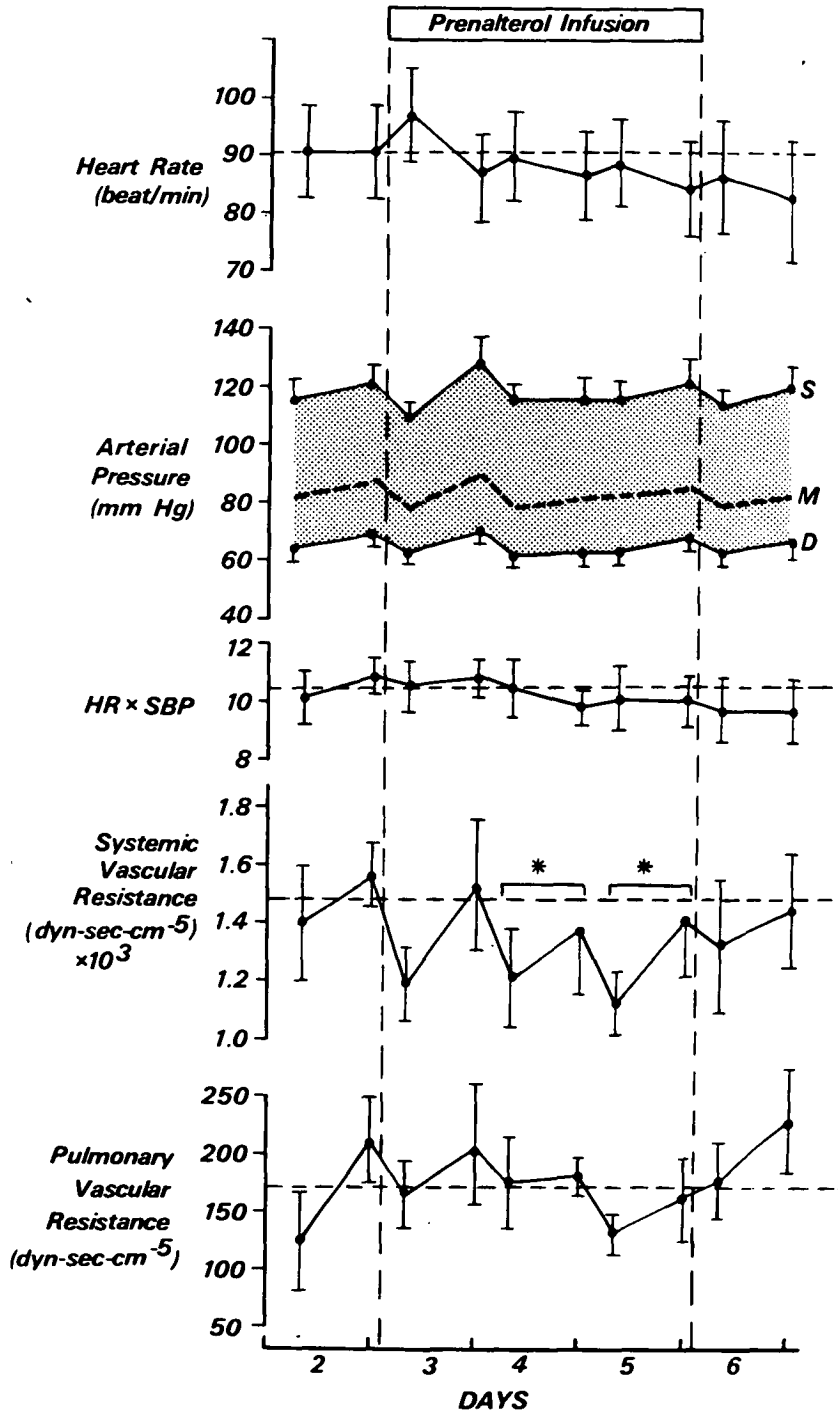
FIGURE 7.3: HAEMODYNAMIC EFFECTS OF PRENALTEROL:



Legend for Figure 7.4:

Haemodynamic variables (mean ± SEM) measured at 1530 and 0830 hrs daily in five patients with heart failure. The discontinuous horizontal lines represent mean "run-in" values. The bars with asterisks indicate significant changes from these levels (* $p<0.05$, ** $p<0.01$). Arterial pressures are plotted as systolic (S), mean (M), and diastolic (D) values. The heart rate by systolic arterial pressure product (HR x SBP) is in arbitrary units.

FIGURE 7.4: HAEMODYNAMIC EFFECTS OF PRENALTEROL:



Comparing data from the "run-in" day and the final infusion day, prenalterol induced clear-cut increments in stroke work index in all patients with concomitant decrements or little change in pulmonary capillary wedge pressure (fig 7.5A). On the contrary, withdrawal of prenalterol resulted in a decline in stroke work index in each case, along with minor and variable changes in wedge pressure (fig 7.5B).

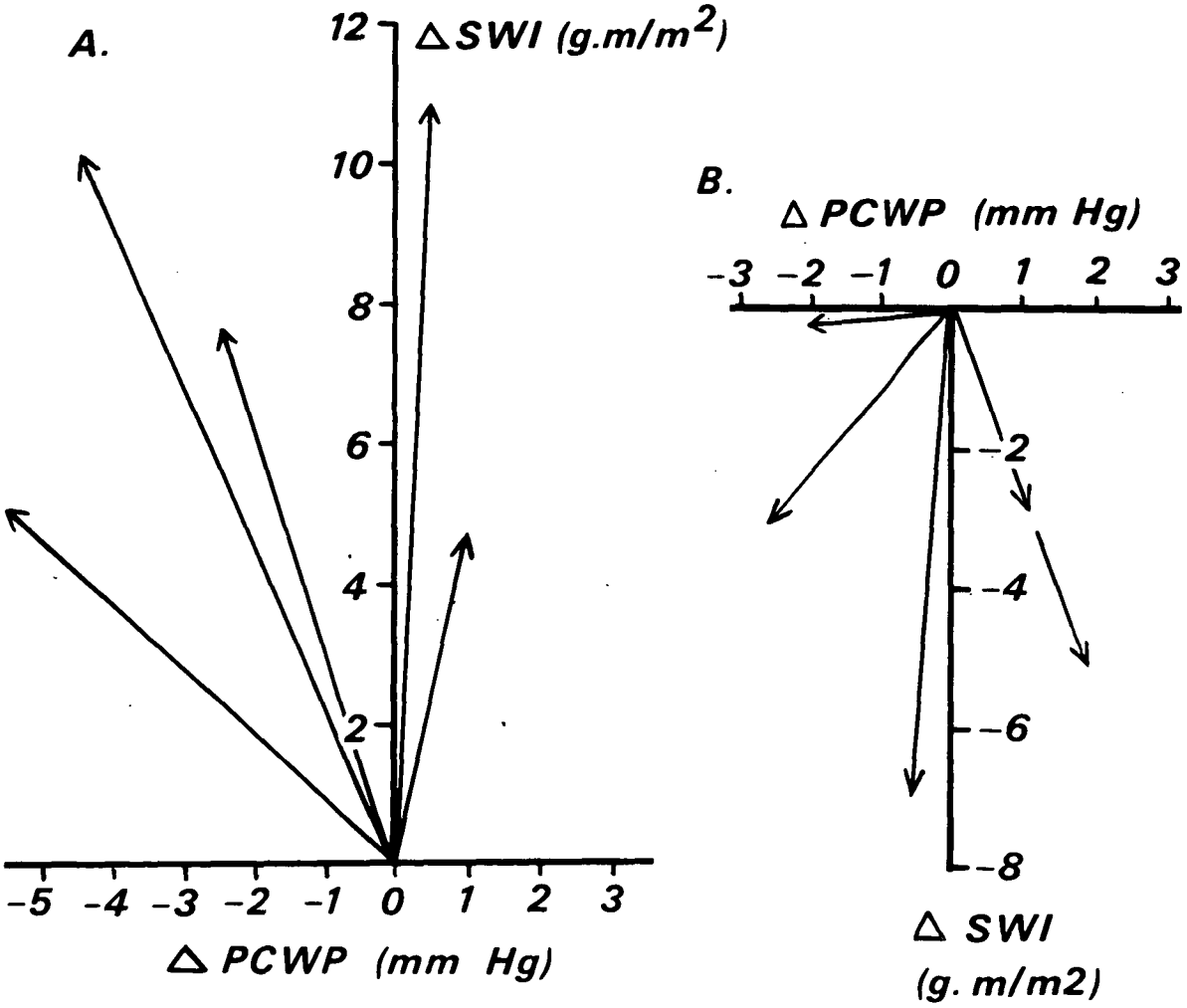
3. Hormone and Electrolyte Responses:

Baseline levels of plasma renin activity, angiotensin II and plasma aldosterone were moderately elevated as might be expected during long-term treatment with diuretics. Prenalterol therapy resulted in a greater than two-fold rise in plasma renin activity and somewhat lesser increments in angiotensin II and plasma aldosterone (fig 7.6). Urine aldosterone increased in a step-wise fashion, and along with plasma renin activity and angiotensin II, tended to decline when prenalterol infusion was ceased (fig 7.6). No change was observed in cortisol levels or in circulating norepinephrine and epinephrine levels (fig 7.6).

Urine sodium excretion tended to decline during prenalterol administration and increased to exceed dietary intake when the drug was withdrawn (fig 7.7). These changes, along with those in body weight (fig 7.7) were not statistically significant. Urine potassium equalled dietary intake before prenalterol, then declined during the three days of infusion, and subsequently returned to baseline (fig 7.7). While these fluctuations again were not statistically significant, there was a significant rise in plasma potassium concentration on the final two study days (fig 7.7).

Fasting plasma insulin levels increased two-fold during prenalterol administration (fig 7.7). The tendency for fasting glucose levels to rise during the study did not reach levels of statistical significance. No changes in plasma glucagon (216 $\pm$ 36 pg/ml on Day 2; 253 $\pm$ 64 pg/ml on Day 5), or pancreatic polypeptide (318 $\pm$ 78 pg/ml on Day 2; 531 $\pm$ 128 pg/ml on Day 5) were seen.

FIGURE 7.5



Changes in Stroke Work Index (Δ SWI) and in mean pulmonary capillary wedge pressure (Δ PCWP) firstly with the introduction of prenalterol (A), and secondly upon withdrawal of the drug (B). In fig 7.5A, data from the "run-in" day for each patient are compared with that during the third prenalterol infusion day, whilst in fig 7.5B results from the third day of prenalterol administration are compared with the subsequent day after discontinuation of the drug. In fig 7.5B, data from two patients fell on the same line.

Legend for Figure 7.6:

Hormone data before, during, and after prenalterol in five patients with heart failure (mean $\pm$ SEM). The discontinuous horizontal lines represent mean "run-in" (pre-prenalterol) values for each index. Bars with asterisks indicate statistical significance (* $p<0.05$, ** $p<0.01$) compared to "run-in" levels.

FIGURE 7.6: HORMONE EFFECTS OF PRENALTEROL:

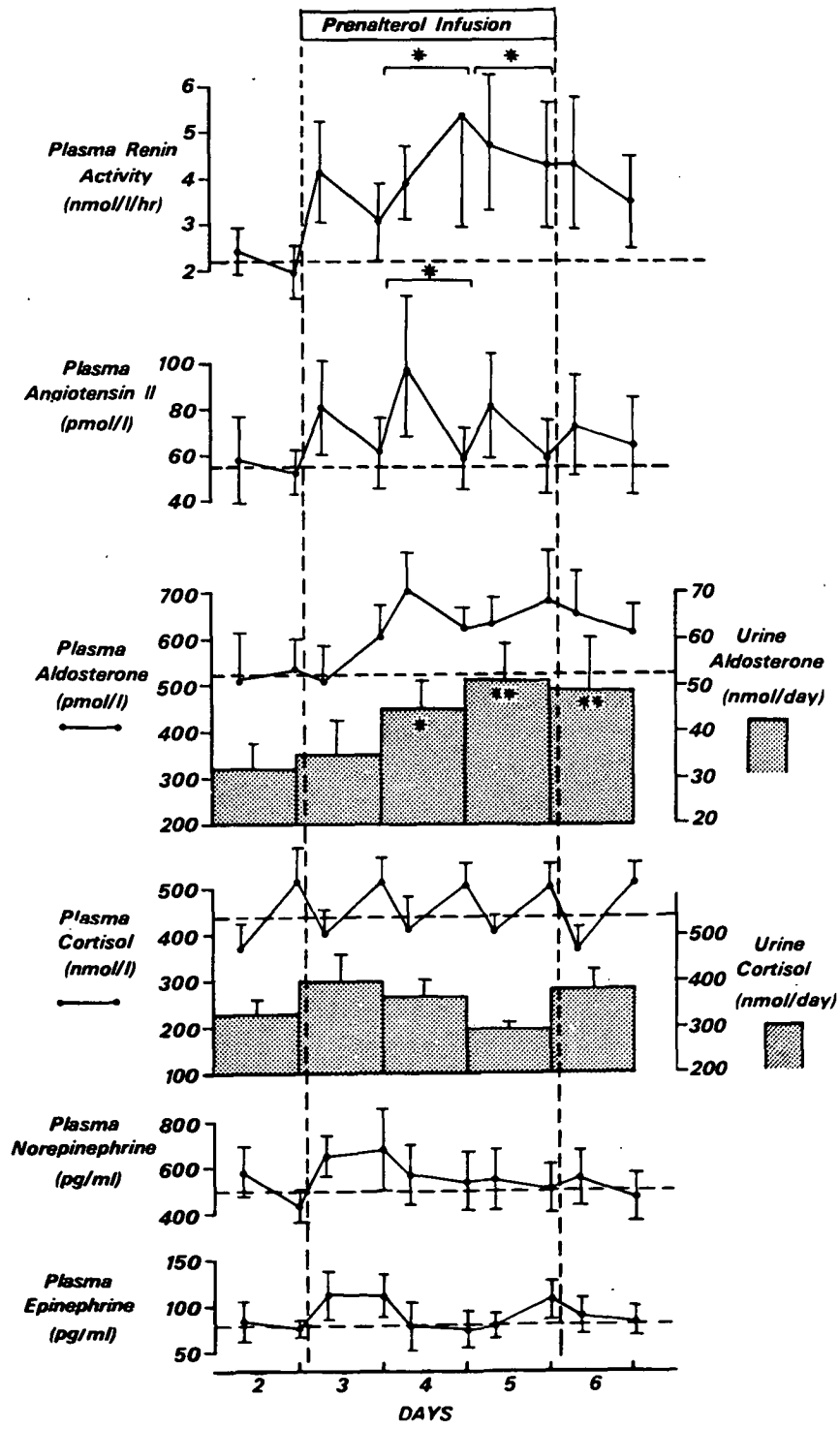
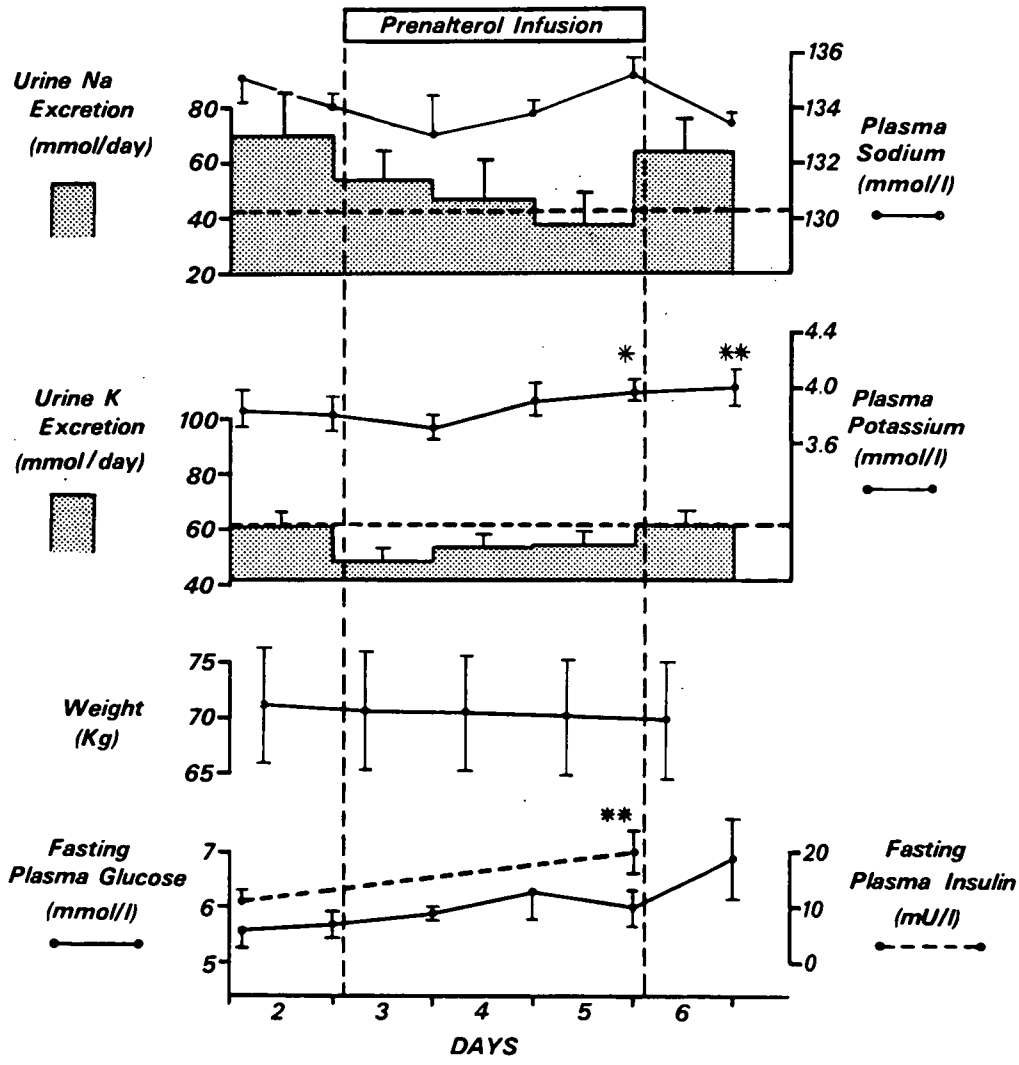


FIGURE 7.7: METABOLIC EFFECTS OF PRENALTEROL:



Electrolyte, body weight, glucose, and insulin data (mean ± SEM) from five patients treated with prenalterol for three days. The mean dietary intakes of sodium and potassium are represented by the discontinuous horizontal lines. (* $p<0.05$, ** $p<0.01$ when data was compared to that on day 2).

Haemodynamic and hormonal responses to prenalterol infusion in Patient 6 have been graphed separately (fig 7.8). Inclusion of his results in the data analysis enhanced the levels of significance already reported.

4. Dose Response Data:

Dose response data are available for the five patients studied at each of the three infusion rates (table 7.3). Infusion at 60, 120, and 240 nmol/min produced steady-state plasma prenalterol concentrations of 52 $\pm$ 3, 121 $\pm$ 6, and 194 $\pm$ 9 nmol/l respectively. Cardiac index, stroke index and forearm blood flow increased in a linear fashion, while pulmonary capillary wedge pressure (PCWP) fell at the lowest infusion rate then remained stable. The increase in plasma renin activity, angiotensin II, and aldosterone plateaued during the second day of prenalterol infusion.

FIGURE 7.8: HAEMODYNAMIC AND HORMONE DATA FOR PATIENT 6:

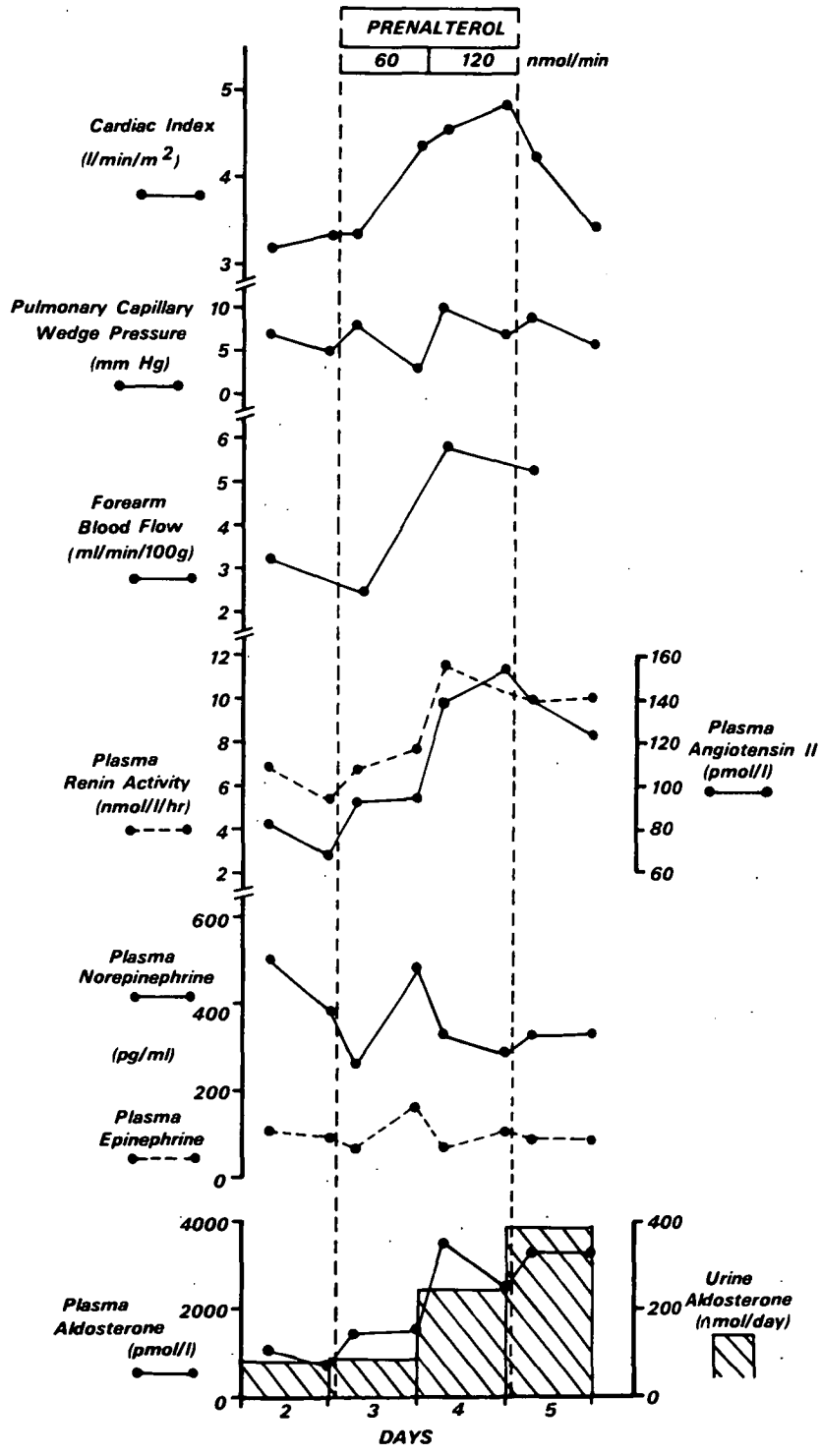


TABLE 7.3: DOSE RESPONSE DATA FROM FIVE PATIENTS:

STUDY DAY	2	3	4	5	6
Infusion Rate (mmol/min)	0	60	120	240	0
Prenalterol steady-state plasma conc. (nmol/l)	-	51.9 ±3.3	121.3 ±6.2	194.0 ±8.5	-
Cardiac Index ($l/min/m^2$)	2.4 ±0.3	2.7 ±0.4	2.8 ±0.4	3.0 ±0.4	2.6 ±0.3
Forearm Bl. Flow (ml/min/100g)	2.9 ±0.7	3.3 ±0.4	3.7 ±0.8	4.0 ±0.6	3.4 ±0.5
Pulm Cap Wedge Press (mm Hg)	13.7 ±1.6	10.5 ±1.7	11.5 ±1.6	11.0 ±1.6	10.7 ±1.4
Plasma Renin Activity (nmol/l/min)	2.2 ±0.6	3.6 ±1.0	4.6 ±1.5	4.5 ±1.5	3.9 ±1.3
Angiotensin II (pg/ml)	55 ±16	71 ±20	77 ±23	70 ±21	69 ±23
Aldosterone (pmol/l)	526 ±93	589 ±74	664 ±70	659 ±84	638 ±78

Mean ± SEM

Haemodynamic and hormonal indices are expressed as daily means.

7.5 DISCUSSION:

Present day therapy of heart failure relies heavily on correction of abnormal fluid accumulation and vascular tone. The primary abnormality in most types of cardiac failure namely, impaired myocardial contractility, is less well managed. Digitalis remains the only agent for chronic ambulant therapy. It is a weak inotropic drug compared to the modern synthetic amines (Goldstein et al, 1980) and its long-term usefulness in patients in sinus rhythm remains controversial (Selzer, 1981).

Prenalterol, a synthetic selective beta-1 agonist is free from several of these disadvantages. Since it can be given orally it is a potential substitute for digitalis for the ambulatory management of cardiac failure (Waagstein et al, 1979). Short term studies have confirmed its inotropic action and freedom from acute toxicity (Svendsen et al, 1980; Hutton et al, 1980; Awan et al, 1981; Kirlin and Pitt, 1981) but there is little data available on the dose-response characteristics of the drug in heart failure patients. Its effect on important neurohumoral systems and electrolytes in cardiac failure required clarification. This information is of crucial importance since the long-term efficacy of the drug will be determined by these changes.

Our study confirms that prenalterol increases cardiac output and stroke work while decreasing the left ventricular filling pressure. This is the hallmark of the action of an inotropic drug in heart failure, although it is virtually impossible to separate vasodilator from inotropic effects of a drug in the intact human (Rude et al, 1981). In isolated heart muscle studies, prenalterol has been shown to have definite inotropic properties (Mattson et al, 1982). Awan et al (1981) have reported that prenalterol induces vasodilatation on the basis of the fall in calculated systemic vascular resistance, and our data support their observations. Furthermore, forearm blood flow measurements confirm vasodilatation in this vascular bed. Vasodilatation has been reported with other inotropic drugs including cardiac glycosides (Mason & Braunwald, 1964), terbutaline (Slutsky, 1981), amrinone (LeJemetel et al, 1979) and pirbuterol (Dawson et al,

1981). This effect is only prominent in cardiac failure patients, being absent in animals and healthy volunteers. Awan et al (1981) suggest that this vasodilatation may be due to the improvement in cardiac output inducing a withdrawal of inappropriately raised sympathetic tone. This study did not address the underlying mechanism, but the lack of any change in circulating catecholamines suggests that sympathetic influences were not major determinants. Another possibility is beta-2 mediated vasodilatation, since prenalterol presumably only has a relatively selective beta-1 agonist activity. The adrenergic receptors located in the heart that regulate myocardial contractile state have been termed beta-1, while those receptors that promote tracheal and vascular smooth muscle relaxation are termed beta-2 (Lands et al, 1967). Controversy, however, surrounds this simplistic classification, as well as the issues of receptor typing according to the end organ, the relative distribution of receptors within an organ and the manner in which compounds may differ in their effects on chrono- and inotropic response, both of which are presumably beta-1 effects (Weber, 1982a). Whatever the reason, the vasodilatation produced by prenalterol is likely to be beneficial since it would tend to offset the vasoconstriction that occurs in cardiac failure. It thus supplements the inotropic action by concomitant afterload reduction.

The haemodynamic effects of prenalterol appeared to be dose-dependent, increasing in a linear fashion and declining rapidly when the infusion was discontinued. Some residual elevation of stroke output remains, which may be of therapeutic significance. In this regard, the persistence of inotropic activity for as long as three months has been reported after dobutamine infusion (Unverforth et al, 1980). Heart rate did not alter significantly with increasing doses of prenalterol confirming the lack of an important chronotropic action. Similarly, there was no change in the arterial pressure and the pressure-rate product, which is an indirect measure of myocardial oxygen demand. This important facet of the drug's action requires confirmation by direct measurement, because the indirect assessment of cardiac oxygen response may be fallacious (Rouleau et al, 1981).

The effects of positive inotropic agents on myocardial oxygen consumption depend on their influence on two major determinants of myocardial oxygen consumption: wall tension and contractility, which change in opposite directions. In individuals with normal cardiac function, drugs that stimulate myocardial contractility elevate oxygen consumption, since heart size and, therefore, wall tension are not reduced and do not offset increased metabolism produced by stimulation of contractility (Braunwald & Sobel, 1980). In the failing dilated ventricle, inotropic agents increase contractility so that the left ventricular end-diastolic pressure and volume fall substantially. On the basis of the Laplace relation (Mirsky et al, 1979), this reduction in volume leads to a reduction in intramyocardial tension, which tends to reduce myocardial oxygen consumption. This fall is offset by the increase in contractility, which tends to augment myocardial oxygen consumption. The net result of these opposing effects produces no change, a small increase, or a small decrease in myocardial oxygen consumption. Thus, the change in myocardial oxygen demand produced by an inotropic agent will depend on the extent to which myocardial tension is reduced in relation to the extent to which the contractile state is augmented (Covell, Braunwald & Ross, 1966; Sonnenblick et al, 1968). Two groups (Kupper et al, 1980; Tweddel et al, 1982) have reported that prenalterol administration to patients with heart failure produces small, but non-significant rises in myocardial oxygen demand determined from myocardial A-V oxygen difference and coronary sinus blood flow measured directly, using the method described by Ganz et al, (1971). One patient, (Kupper et al, 1980) however, increased his myocardial lactate production suggesting that the rise in myocardial oxygen demand in this patient produced significant myocardial ischaemia. Obviously, a chronic increment in contractility may be detrimental in some patients, and more research is required to enable recognition of such patients.

Isoprenaline is a potent, nonspecific beta-adrenoceptor agonist that provokes a considerable rise in heart rate and can precipitate arhythmias (Loeb et al, 1973). Similarly, dopamine and dobutamine also produce ventricular arrhythmias (Kersting et al, 1976; Golberg et al, 1977). Increased ventricular ectopy (Kirlin & Pitt, 1981) following prenalterol therapy has been reported in some patients, but this is

matched by other reports of no such adverse effects (Tweddel et al, 1982; Awan et al, 1981). We did not observe a significant increase in ventricular ectopy, but further research is required to determine the safety of oral therapy with regard to the production of lethal arrhythmias.

This study demonstrates activation of the juxtaglomerular apparatus with release of renin during prenalterol infusion. Since stimulation of beta-1 receptors has been shown to augment renin release (Himori et al, 1979; Kopp et al, 1980) , this effect of prenalterol is not surprising. That this action of prenalterol may be physiologically important is confirmed by concomitant increments in plasma angiotensin II and aldosterone levels. There are several important questions raised by these data. Firstly, cardiac function was maintained and even enhanced despite the vasoconstrictor action of angiotensin II. This suggests that the inotropic and vasodilating actions of prenalterol were sufficiently powerful to overcome any increase in afterload, at least in the short term. Secondly, it is not clear whether activation of the renin-angiotensin-aldosterone system is sustained during long-term therapy. If it were, then a decline in cardiac output due to increased afterload and accumulation of fluid secondary to elevated aldosterone levels may occur leading ultimately to blunting or a loss of therapeutic response.

Long-term studies using oral therapy are required to determine whether tolerance to therapy occurs. The data presented here would suggest that activation of the renin-angiotensin-aldosterone system, if sustained, may well lead to tolerance and this will need to be investigated. Blockade of the renin-angiotensin system by means of a converting-enzyme inhibitor may then be required to maintain the initial therapeutic effect. Attenuation of the haemodynamic effects of pirbuterol (a beta-2 agonist) have recently been associated with "down-regulation" of beta-receptors (Colucci et al, 1980b). These researchers report a decrease in lymphocyte beta-adrenoceptor density in these patients. However, other mechanisms for the attenuation of effect were not looked at. The effect on lymphocyte beta-receptors probably does not represent changes in myocardial receptors, so other mechanisms,

such as activation of the renin-angiotensin-aldosterone system may have produced the attenuation of pirbuterol effect. As outlined in Chapter 1, the failing heart's ability to respond to synthetic catecholamines is preserved in contrast to a damped response to sympathetic nerve stimulation (Covell et al, 1966; Goldstein et al, 1975). Presumably, myocardial beta-receptor density is enhanced, although the opposite was found in patients with severe pre-terminal heart failure undergoing cardiac transplantation (Bristow et al, 1982).

Oral prenalterol may improve exercise performance (Waagstein et al, 1979). Another group demonstrated greater short-term improvement in haemodynamics during exercise than at rest (Tweddel et al, 1982). Systemic vascular resistance during exercise was reduced by 20%, but only 11% at rest. Although I was unable to demonstrate that the decline in systemic vascular resistance at rest was related to a decline in sympathetic activity (as judged by circulating catecholamine levels), this effect may be more apparent during exercise. Enhanced activity of the sympathetic nervous system during exercise provides inotropic support for the failing myocardium, while concomitant peripheral vasoconstriction (alpha-receptor activation) has a detrimental effect (Higgins et al, 1972). From a theoretical point of view, an improvement in cardiac output during exercise induced by selective beta-1 stimulation should reduce peripheral sympathetic activity, thereby reducing vascular resistance to a greater extent during exercise, improving muscle blood flow and enhancing exercise capacity.

Beta receptors modulate the release of many hormones including those concerned with glucose homeostasis. A significant rise in plasma insulin levels was observed during the present study. Animal data suggest that the adrenergic receptors responsible for enhancing insulin secretion are beta-2 in type (Miller, 1981). Ronn et al (1980) observed an increase in insulin during prenalterol administration in normal volunteers, together with the observations in this study, suggest either that stimulatory beta-1 receptors exist on the pancreatic beta cell, or that prenalterol has sufficient beta-2 agonist action to release insulin. Alternatively, prenalterol may primarily increase blood glucose levels by enhancing gluconeogenesis, thereby increasing release

of endogenous insulin. Although we saw no significant change in glucose, glucagon or pancreatic polypeptide levels it would appear prudent to monitor blood glucose during future long-term studies of prenalterol, especially in diabetics. Since insulin reportedly increases myocardial contractility in cardiac failure (Farah & Aloussi, 1981) it is interesting to speculate whether the increase in plasma insulin observed in this study contributed to the inotropic effect of prenalterol.

7.6 CONCLUSION:

Prenalterol infusion in six patients with heart failure increased cardiac index and stroke index in a dose-response fashion without adversely affecting heart rate, arterial pressure or right-heart pressures. Forearm blood flow rose in a step-wise fashion during the incremental infusion of prenalterol. Activation of the renin-angiotensin-aldosterone axis was observed, and if sustained during long-term oral prenalterol treatment could serve to negate, in part, the beneficial haemodynamic effects.

CHAPTER 8

THE STABILITY OF HAEMODYNAMIC AND HORMONAL PARAMETERS, AND THEIR INTER-RELATIONSHIPS IN HEART FAILURE:

8.1 INTRODUCTION:

Although haemodynamic and hormonal inter-relationships have been studied extensively in cardiac failure (Levine et al 1982b, Kluger et al 1982, Curtiss et al 1978, Dzau et al 1981), there are few reports of "baseline" controlled observations extending beyond a few hours. As well as providing insight into spontaneous variations of cardiac and hormonal function, this information is required to interpret drug intervention studies using invasive techniques, where the effects of bed rest, circadian rhythm, concurrent drug therapy and stress due to catheterisation and unfamiliar surroundings are all too often ignored.

For a period up to 24 hours after cardiac catheterisation and bedrest, haemodynamic and hormone indices vary significantly (Maslowski et al, 1981a; Thaulow et al, 1982). To date, the stability of these parameters over longer periods of time has not been reported. In this chapter, I document the variation in cardiac function and hormone levels measured over a 48 hour period in twenty-one patients studied under basal conditions. The effects of NYHA Functional Class, diuretic therapy, diet, sodium balance, aetiology and cardiac rhythm on haemodynamic, hormonal and electrolyte indices were then assessed, along with relationships between these parameters.

8.2 METHODS:

1. General:

The control data from fifteen patients included in the previous two chapters are analysed here in greater detail. To enhance patient numbers, the control data from a previous study performed in this unit (Maslowski et al, 1981a) were included. I was not involved in this investigation, which documented the effect of captopril in six patients with stable heart failure, however a similar protocol was followed, with haemodynamic and hormonal measurements being performed at identical times (0830 and 1530 hrs).

2. Patients:

The clinical details of the twenty-one patients are summarised in Table 8.1. They were accepted for study only if their clinical state was stable for one month prior to investigation. All patients gave informed consent, with each study protocol having been approved by the Hospital's Ethical Committee. Left ventricular failure resulted from ischaemic heart disease in fourteen patients, and dilated cardiomyopathy in seven patients. In all but two patients, a definitive diagnosis was established or confirmed by cardiac catheterisation (seventeen patients) or post mortem examination (two patients). Dilated cardiomyopathy was diagnosed according to the criteria of Goodwin and Oakley (1972). Seven patients were in NYHA Functional Class II, eight were in Class III and six were in Class IV. Left ventricular radionuclide ejection fraction varied from 8 to 32% (mean = 21%). Six patients were in atrial fibrillation, while the remainder were in sinus rhythm. No patient was oedematous at the time of study. Digoxin (0.125 to 0.25 mg/day) and frusemide (40 to 1000 mg/day) therapy remained unchanged throughout the period of study, but other drugs were withdrawn at least five days before the study.

TABLE 8.1 CLINICAL DATA:

Patient	Sex	Age	NYHA Class	LVEF (%)	Frusemide Dose (mg)	Aetiology	Rhythm
1*	M	63	III	-	500	IHD	SR
2*	F	72	IV	-	1000	IHD	AF
3*	M	54	IV	26	250	IHD	SR
4*	M	63	IV	29	250	IHD	SR
5*	M	65	III	19	120	IHD	AF
6*	M	72	IV	21	1000	IHD	AF
7 †	M	57	II	25	80	DCM	SR
8 †	M	62	II	18	40	DCM	AF
9 †	M	48	III	24	80	IHD	SR
10 †	M	59	II	11	40	IHD	SR
11 †	M	48	III	26	250	IHD	AF
12 †	M	70	IV	24	160	DCM	SR
13 †	M	61	III	8	500	IHD	SR
14 †	M	58	III	32	160	IHD	SR
15 †	F	66	IV	15	250	IHD	SR
16 ‡	M	46	II	17	500	DCM	SR
17 ‡	M	60	III	14	120	IHD	SR
18 ‡	M	54	II	22	80	DCM	SR
19 ‡	M	58	II	13	80	DCM	AF
20 ‡	M	53	II	28	120	DCM	SR
21 ‡	M	60	III	23	200	IHD	SR

LVEF = left ventricular ejection fraction;
IHD = ischaemic heart disease; DCM = dilated cardiomyopathy;
SR = sinus rhythm; AF = atrial fibrillation.

* = Maslowski et al, 1981a

† = Chapter 6

‡ = Chapter 7

3. Protocol:

Throughout the two day period of study and for at least one day prior to its initiation, each patient received a diet of constant sodium and potassium content (K = 42 to 80 mmol/day). Twelve patients received a low sodium diet (Na = 19 to 48 mmol/day), while nine received a normal sodium diet (Na = 91 to 106 mmol/day). Meals were served at 0915 hr, 1215 hr and 1815 hr. All urine was collected on ice for electrolyte and hormone analysis.

The patients remained semi-supine throughout. Patients 7 to 21 were catheterised on the afternoon prior to the first day of study, while patients 1 to 6 were catheterised on the morning (0800 hr) of the first day. A triple lumen Swan-Ganz catheter was placed in the pulmonary artery for right heart pressure and cardiac output measurements, and a radial or brachial artery cannula was inserted for pressure recordings and blood sampling for determination of plasma hormone levels. Measurements were performed twice daily at 0830 hr and 1530 hr. In patients 7 to 15, further measurements were performed on the second control day at 1000, 1100, 1300, 1500, 1700, 1900 and 2100 hrs.

Blood was drawn at 0830 hr daily for sodium and potassium measurements (flame photometry). Plasma ADH levels were determined at 1130 hr in patients 7 to 15 but in patients 16 to 21, measurements were made at 0830 hr, thus time-matched measurements for plasma ADH and sodium concentration were not obtained. Digoxin and frusemide were administered after completion of the 0830 hr recordings.

4. Statistics:

To assess daily and diurnal variation, repeated measures analyses of variance were performed for all variables using programme P2V of the BMDP statistics package. The patients were then grouped according to their NYHA functional classification, dose of frusemide ("Low" -160 mg/day or less; "High" - greater than 160 mg/day), aetiology (ischaemic heart disease or dilated cardiomyopathy), cardiac rhythm (sinus or atrial fibrillation) and dietary sodium intake (low: 19 to 48 mmol/day; normal: 91 to 106 mmol/day). The effect of natriuresis following strict bed-rest was assessed by arbitrarily dividing the patients into two groups according to the difference between urinary excretion and dietary intake: "natriuresis" > 20 mmol/day; "balance" < 20 mmol/day.

Results are presented as mean $\pm$ standard error of the mean (SEM) unless stated otherwise. To remove the possible effect of stress from unfamiliar surroundings and recent catheterisation, mean values from 0830 and 1530 hr recordings on the second day were used in the calculation of correlation coefficients.

8.3 RESULTS:

1. General:

In considering the spontaneous variation of hormonal and haemodynamic parameters, the data from patients 1 to 6 were considered separately because measurements were commenced soon after catheterisation. For all other analyses, data from all patients were considered together, with greater emphasis being placed on the second day of measurements.

2. Spontaneous Variation:

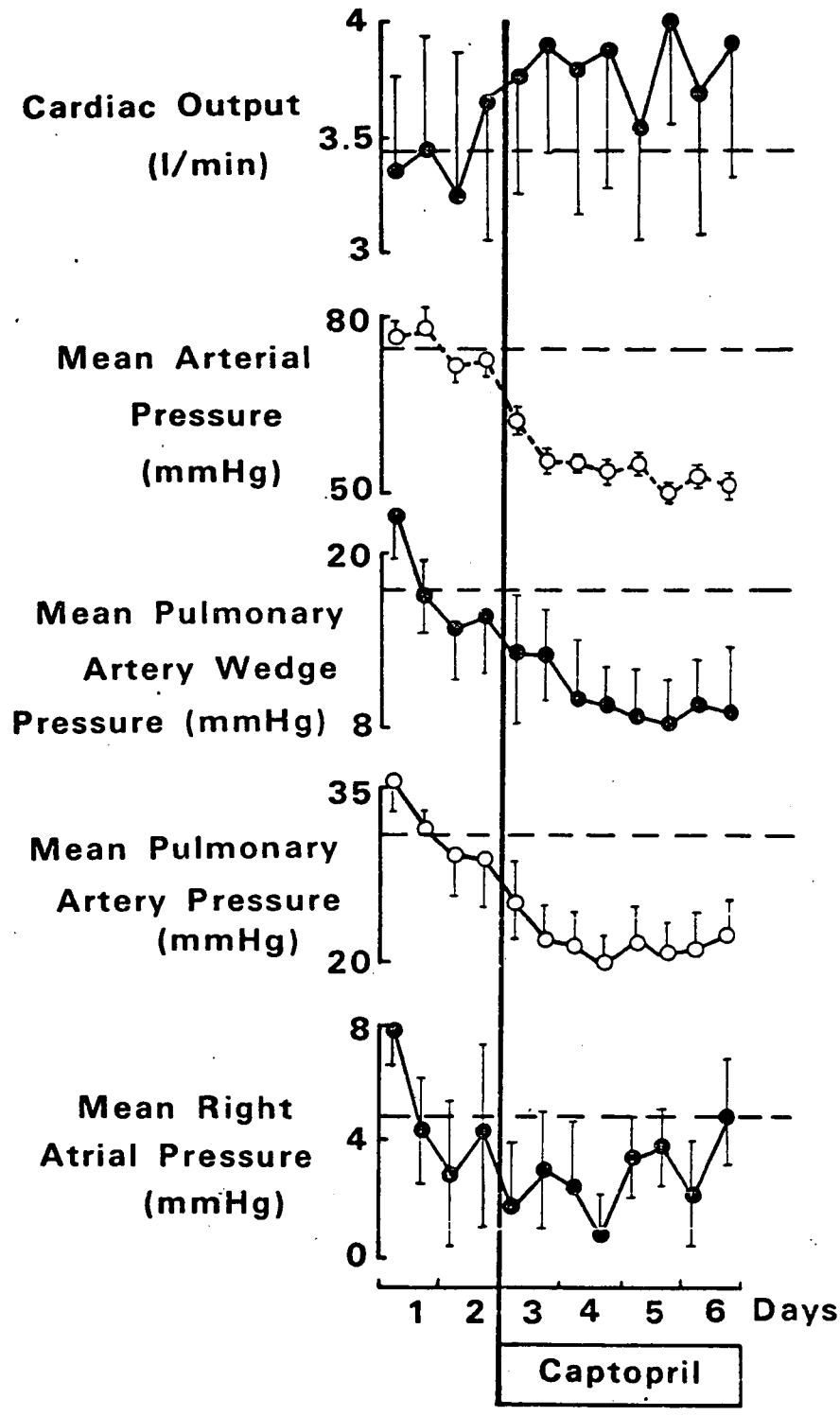
1. Measurements from Patients 1 to 6:

Comparing daily means for Day 1 and Day 2, cardiac index increased slightly from 1.65 $\pm$ 0.21 l/min/m^2 to 1.73 $\pm$ 0.24 l/min/m^2 (NS), while mean pulmonary artery pressure (38.9 $\pm$ 5.3 mm Hg to 33.7 $\pm$ 5.4 mm Hg), left ventricular filling pressure (23.3 $\pm$ 1.8 to 20.8 $\pm$ 2.1 mm Hg) and right atrial pressure (9.1 $\pm$ 3.6 mm Hg to 7.0 $\pm$ 3.4 mm Hg) declined significantly ($p<0.05$). There was little variation in levels of plasma renin activity, angiotensin II or aldosterone, however plasma epinephrine (150 $\pm$ 67 pg/ml to 99 $\pm$ 27 pg/ml) and cortisol (574 $\pm$ 126 nmol/l to 491 $\pm$ 74 nmol/l) did decline, but these changes did not achieve conventional levels of significance. Graphical display of this data is provided in figures 8.1 and 8.2 along with the response to captopril in these patients (from Maslowski et al, 1981a).

2. Day 1 versus Day 2:

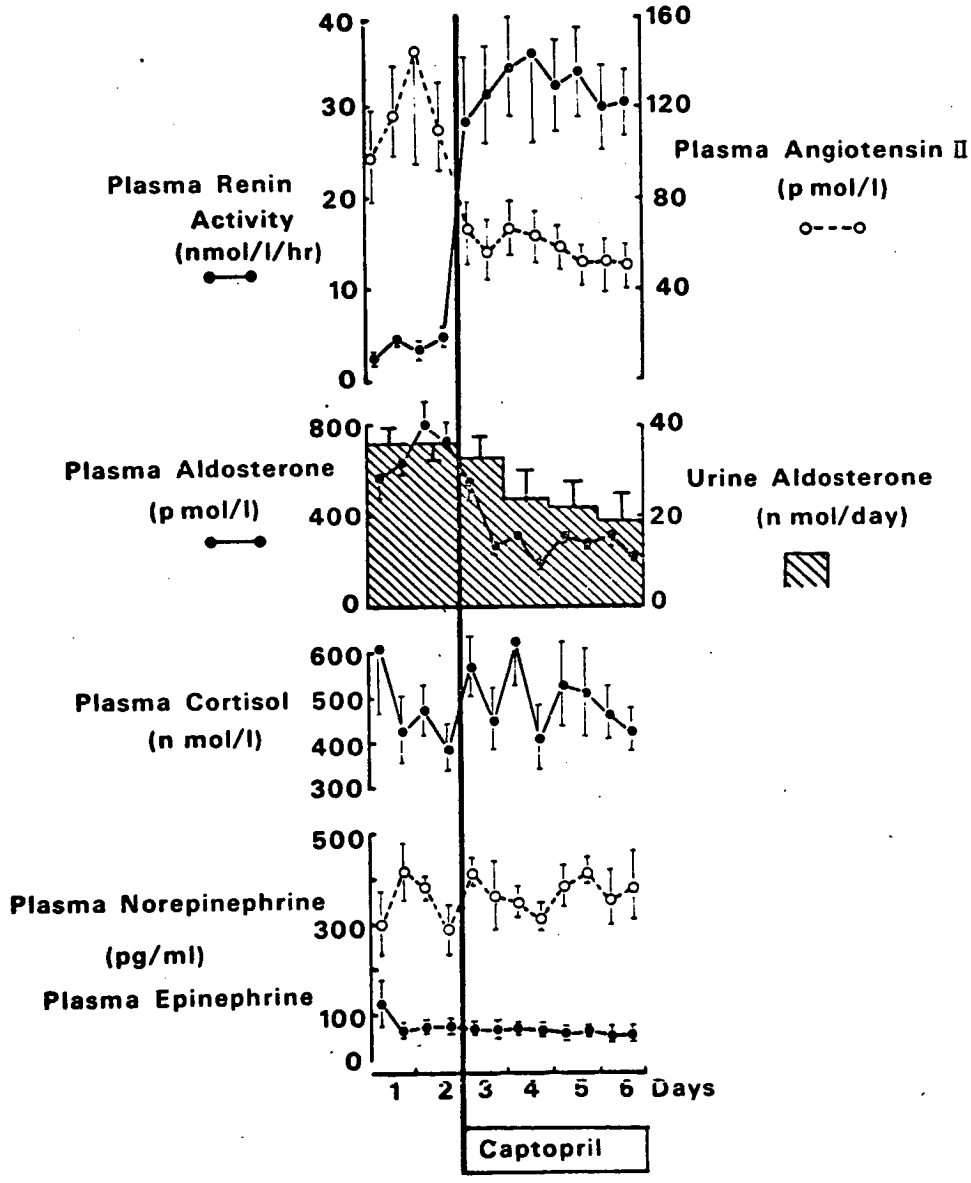
For those patients (7 to 21, n = 15) in whom measurements commenced at least twelve hours after catheterisation, haemodynamic indices were not significantly different on Day 1 compared to Day 2 (Table 8.2). Plasma

FIGURE 8.1:



Haemodynamic measurements before and during captopril therapy in five patients with resistant heart failure (mean ± SEM) (From Maslowski et al, 1981a).

FIGURE 8.2:



Hormone indices measured before and during captopril treatment in five patients with resistant cardiac failure. Results are expressed as mean + SEM (from Maslowski et al, 1981a).

renin activity and urine aldosterone excretion were higher on the second day ($p<0.001$, $p<0.05$ respectively), while plasma epinephrine, body weight, plasma sodium and urinary sodium excretion were significantly lower ($p<0.05$) (Table 8.3).

3. Diurnal Variation:

Cardiac index was significantly higher at 1530 hr than at 0830 hr ($p<0.01$), while plasma cortisol was lower at 1530 hr ($p<0.05$). Results from more frequent observations in nine patients from the second day are shown in Fig 8.3. Cardiac index was generally lowest at the 0830 hr recording, and appeared to rise after meals. The renin-angiotensin-aldosterone system was mildly activated after the administration of frusemide and digoxin given at 0900 hr, however the changes observed did not reach conventional levels of statistical significance. Systemic arterial pressure remained steady throughout (fig 8.3).

TABLE 8.2 SPONTANEOUS VARIATION OF HAEMODYNAMIC DATA IN 15 PATIENTS STUDIED AT LEAST 12 HOURS AFTER CATHETERISATION:

	Day 1		Day 2		Significance	
	0830	1530	0830	1530	1. v 2.	am v pm
Cardiac Index ($l/min/m^2$)	2.45 ±0.16	2.69 ±0.14	2.40 ±0.13	2.48 ±0.14	NS	<0.005
Syst. Press. (mm Hg)	125 ±6	127 ±7	128 ±7	122 ±6	NS	NS
Diast. Press. (mm Hg)	69 ±2	69 ±4	72 ±3	68 ±3	NS	NS
Mean Art. Press. (mm Hg)	87 ±3	89 ±4	91 ±4	86 ±4	NS	NS
Mean PA Press. (mm Hg)	24.1 ±1.4	24.1 ±1.4	24.7 ±1.7	25.3 ±1.8	NS	NS
PAEDP (mm Hg)	15.9 ±1.4	16.1 ±1.4	16.5 ±1.7	17.3 ±1.8	NS	NS
R Atrial Press. (mm Hg)	5.8 ±1.1	5.5 ±1.0	5.9 ±1.1	8.0 ±1.0	NS	NS
Ventricular Rate (bt/min)	83 ±6	85 ±5	87 ±4	87 ±5	NS	NS
Body Weight (Kg)	70.8 +2.6		70.4 +2.5		<0.05	

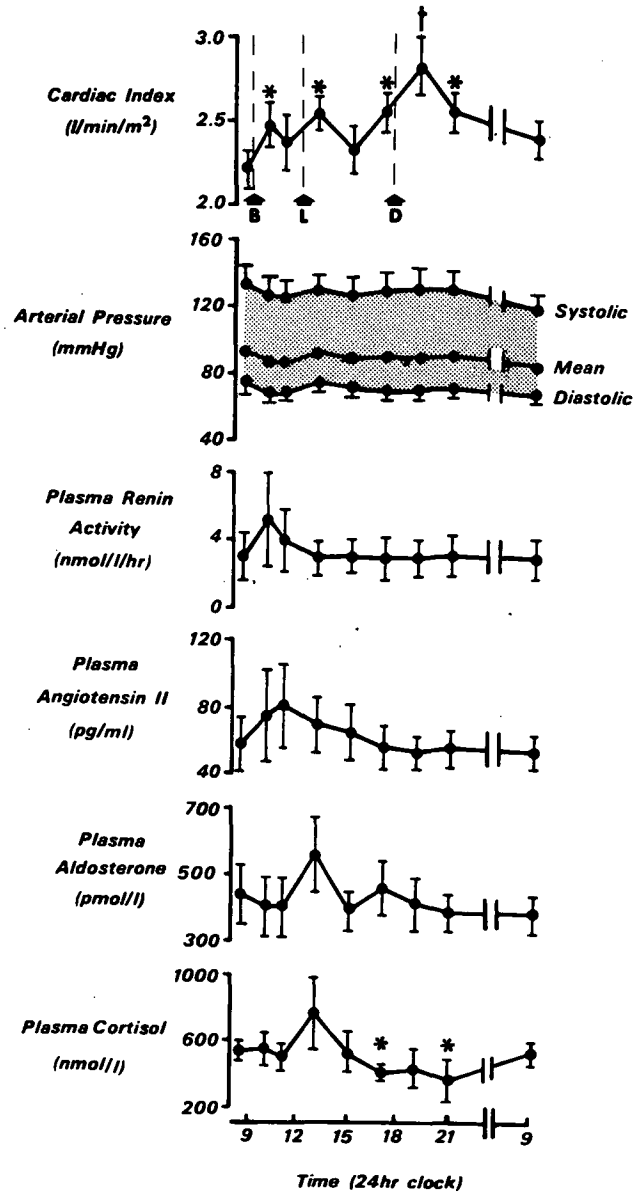
Results are expressed as mean ± standard deviation.
NS = not significant, PAEDP = pulmonary artery end-diastolic pressure, PA = pulmonary artery.

TABLE 8.3: SPONTANEOUS VARIATION OF HORMONE AND ELECTROLYTE DATA IN 15 PATIENTS STUDIED AT LEAST 12 HOURS AFTER CATHETERISATION:

	Day 1		Day 2		Significance	
	0830	1530	0830	1530	1. v 2.	am v pm
PRA (nmol/l/hr)	2.11 ±0.58	2.17 ±0.55	2.59 ±0.72	2.92 ±0.66	<0.005	<0.05
Angiotensin II (pg/ml)	48.9 ±7.2	59.8 ±9.0	55.6 ±8.1	61.5 ±10.2	NS	NS
Aldosterone (pmol/l)	403 ±49	410 ±60	451 ±61	489 ±77	NS	NS
Cortisol (nmol/l)	521 ±50	450 ±67	539 ±50	467 ±64	NS	<0.05
ADH (pg/ml)	5.1 ±4.6		4.6 ±3.8		NS	-
Urine Aldo. Excr. (nmol/day)	23.9 ±3.7		30.7 ±5.1		<0.05	-
Urine Cort. Excr. (nmol/day)	335 ±34		319 ±32		NS	-
Norepinephrine (pg/ml)	568 ±62	594 ±73	500 ±64	607 ±89	NS	NS
Epinephrine (pg/ml)	146 ±28	128 ±18	128 ±36	109 ±18	<0.05	NS
Plasma Na (mmol/l)	135.9 ±0.8		134.7 ±0.8		<0.05	-
Urine Na Excr. (mmol/day)	107 ±10		89 ±11		<0.05	-

Results are expressed as mean ± standard deviation.
NS = not significant, PRA = plasma renin activity,
ADH = anti-diuretic hormone.

FIG 8.3: FREQUENT RECORDINGS IN NINE PATIENTS:

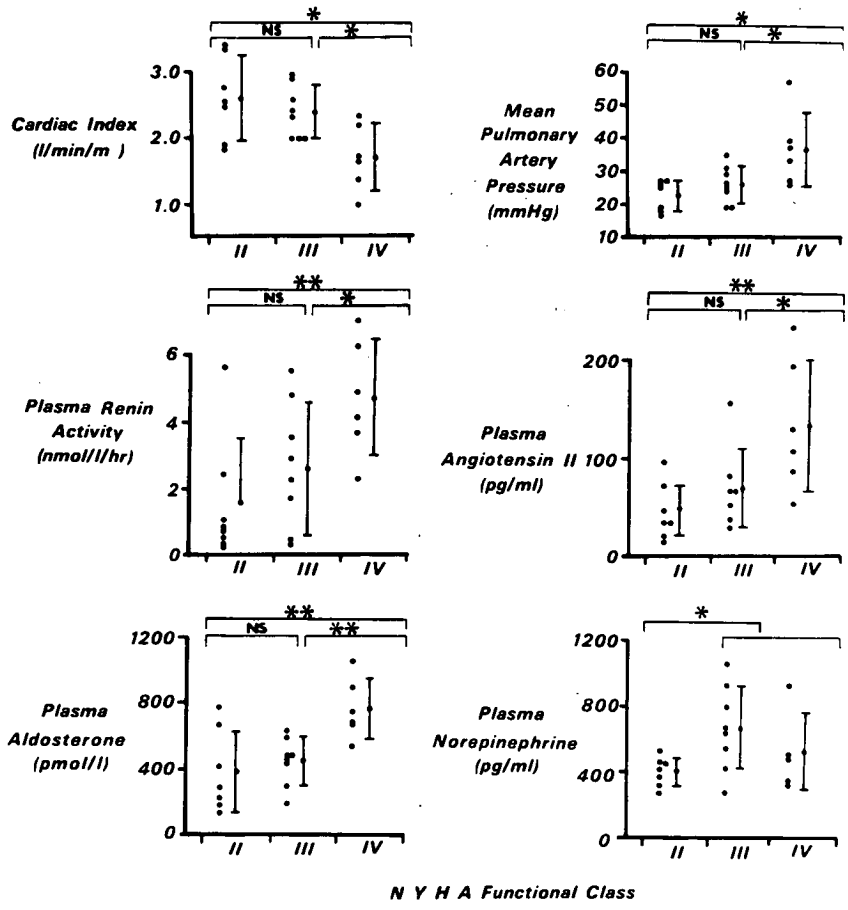


Haemodynamic and hormone indices measured nine times during a 24 hr period in nine patients. Meal hours are indicated as follows: B = breakfast; L = lunch; D = dinner. Significant changes from the first 0830 hr recording for each variable are shown by the symbols: * $p<0.05$; † $p<0.01$.

3. Effects of NYHA Functional Class:

Analysis of variance for NYHA Functional Class and time of measurement demonstrated clear cut differences between the classes for cardiac index, mean pulmonary artery pressure, plasma renin activity, angiotensin II and aldosterone levels, with no interaction with time of measurement. The mean of four measurements for each patient, along with group means, are illustrated in fig 8.4. Compared with Class II and III, cardiac index was lower in Class IV while plasma renin activity, angiotensin II, aldosterone and mean pulmonary artery pressure were higher. Although lower levels of plasma norepinephrine were observed in Class II patients, there was considerable overlap between the groups (fig 8.4), thus analysis of variance produced no significant difference overall. However levels in Class II were lower than those in combined Class III and IV as assessed by Student's t-test ($p<0.05$). Plasma ADH levels were slightly higher in Class III and IV patients when compared to Class II patients (6.1 ± 1.5 pg/ml compared with 4.0 ± 2.0 pg/ml respectively), but the difference was not significant.

FIG 8.4: EFFECT OF NYHA CLASS ON HAEMODYNAMIC & HORMONE PARAMETERS:



For each class, the group mean ± standard deviation are plotted along with mean for each patient (four values/patient).

* $p<0.05$, ** $p<0.01$, NS not significant.

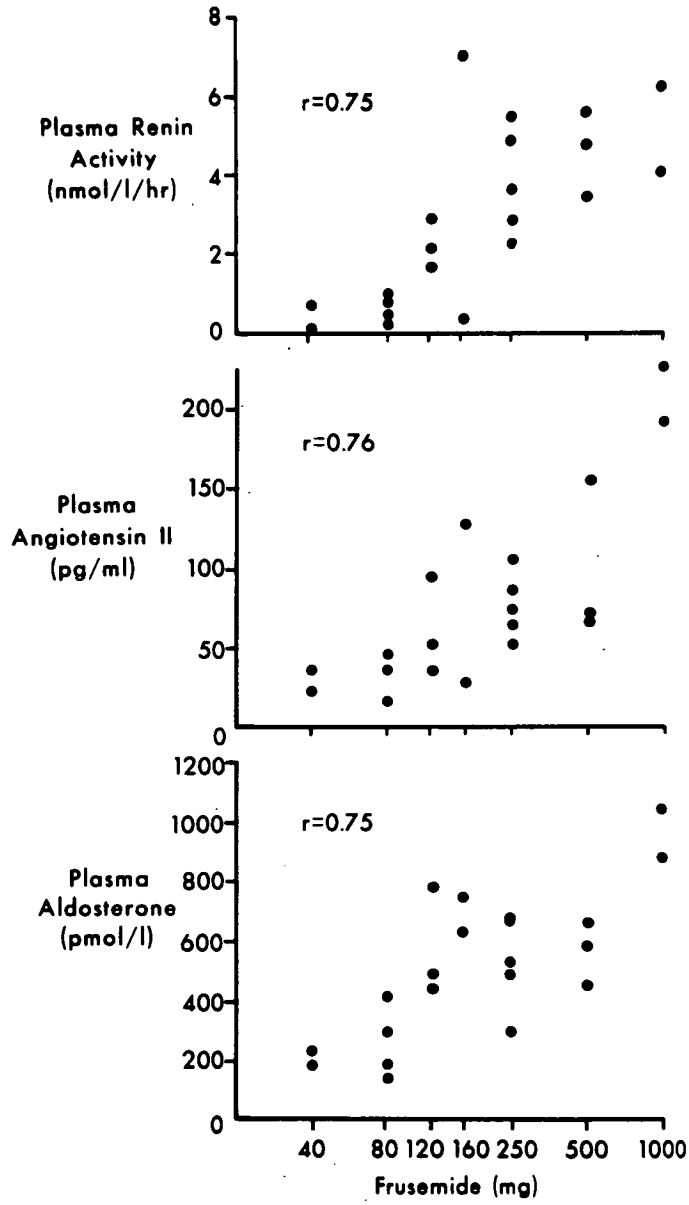
4. Effect of Frusemide Dose:

When the patients were separated into low dose ($\leq$160 mg/day, n = 11) and high dose (>160 mg/day, n = 10) groups, significantly greater activation of the renin-angiotensin-aldosterone system was apparent in the high dose group. Comparing the mean of four measurements for each patient over two days, plasma renin activity was 1.1 $\pm$ 0.3 nmol/l/hr for the low dose and 4.3 $\pm$ 0.7 nmol/l/hr ($p<0.005$) for the high dose group, while plasma angiotensin II levels were 43.5 $\pm$ 7.4 pg/ml and 106 $\pm$ 21.4 pg/ml ($p<0.01$), plasma aldosterone levels were 353 $\pm$ 63 pmol/l and 645 $\pm$ 86 pmol/l ($p<0.001$), and urinary aldosterone excretion levels were 21.4 $\pm$ 3.9 mmol/day and 34.6 $\pm$ 4.6 mmol/day ($p<0.05$) for low and high dose groups respectively. Plasma ADH was also significantly greater in the high dose group (7.1 $\pm$ 1.5 pg/ml compared to 3.0 $\pm$ 0.7 pg/ml, $p<0.05$).

Close correlation was observed between frusemide dose (log transformation) and plasma renin activity, angiotensin II and aldosterone levels ($r=0.75$; $r=0.76$; $r=0.75$ respectively, $p<0.001$) (fig 8.5). A weaker relationship between plasma ADH levels and log frusemide dose was also observed ($r=0.55$, $p<0.05$). Note that each point on these graphs represents the mean of two measurements performed on the second day.

FIG 8.5:

FRUSEMIDE INDUCED ACTIVATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM



These graphs demonstrate the relationship of plasma renin activity, plasma angiotensin II, and aldosterone to frusemide dosage (log transformation). Each data point represents the mean of two measurements on the second day for each hormone.

5. Effect of Metabolic Balance:

1. Dietary Sodium Intake:

Twelve patients received a "low" sodium diet (19 to 48 mmol/day) while nine received a "normal" diet (91 to 106 mmol/day). The functional status, and frusemide dosage for the two groups were similar. Plasma aldosterone levels and urinary aldosterone excretion were higher in the "low" sodium group than in the "normal" sodium group (624 $\pm$ 84 pmol/l versus 381 $\pm$ 84 pmol/l and 35.1 $\pm$ 4.4 mmol/day versus 20.7 $\pm$ 4.2 mmol/day respectively, $p<0.05$). Plasma renin activity and angiotensin II levels were elevated in the low sodium group, but these differences did not reach levels of statistical significance (3.2 $\pm$ 0.6 nmol/l/hr versus 2.4 $\pm$ 1.0 nmol/l/hr and 96 $\pm$ 22 pg/ml versus 58 $\pm$ 13 pg/ml respectively). Other hormonal and haemodynamic parameters were not influenced by dietary sodium intake.

2. Degree of Natriuresis:

The degree of natriuresis appeared to be unrelated to NYHA Functional Class or diuretic dosage. There were no differences in haemodynamic or hormonal indices between the group of patients with significant natriuresis (see methods), and those patients in sodium balance. However, weight loss was higher in the former group ($p<0.05$).

6. Effect of Aetiology:

No differences in haemodynamic or hormonal variables were evident on the basis of aetiology (ischaemic versus idiopathic cardiomyopathy).

7. Effect of Cardiac Rhythm:

Compared with patients in sinus rhythm, those patients in atrial fibrillation had a lower cardiac index (1.68 ± 0.20 l/min/m^2 compared to 2.51 ± 0.14 l/min/m^2, $p<0.005$) and heart rate ($p<0.05$), while pulmonary artery end-diastolic pressure (21.3 ± 2.6 mm Hg versus 16.8 ± 1.5 mm Hg) and right atrial pressure (9.7 ± 3.2 mm Hg versus 5.7 ± 1.1 mm Hg) were significantly higher ($p<0.05$). No hormone or electrolyte differences were noted.

8. Hormone and Electrolyte Relationships:

For the twenty-one patients, mean results from the second day of recordings were taken for calculation of correlation coefficients. Plasma aldosterone correlated very closely with plasma renin activity ($r=0.72$, $p<0.001$) and plasma angiotensin II ($r=0.70$, $p<0.001$). Furthermore, plasma angiotensin II correlated significantly with plasma renin activity ($r=0.65$, $p<0.01$). The relationship of plasma aldosterone with plasma potassium was negative ($r=-0.11$) and with plasma cortisol was positive ($r=0.33$), but neither reached levels of statistical significance.

Positive, but non-significant correlations were observed between plasma renin activity and concurrently measured plasma norepinephrine ($r=0.35$) and epinephrine levels ($r=0.41$, $0.10<p<0.05$). Likewise, the negative relationships between plasma sodium and plasma renin activity ($r=-0.33$), plasma angiotensin II ($r=-0.34$) and ADH ($r=-0.07$) were not significant.

Plasma angiotensin II correlated closely with plasma creatinine ($r=0.55$, $n=20$, $p<0.01$) and plasma urea ($r=0.69$, $p<0.005$) while plasma renin activity and plasma aldosterone showed similar significant, but weaker correlations. No significant association between plasma ADH levels ($n=15$) and plasma sodium ($r=-0.07$), angiotensin II ($r=0.14$), or norepinephrine ($r=0.19$) was observed.

9. Hormone & Haemodynamic Relationships: (Table 8.3)

As in section 8, mean results from the second day of recordings were taken for calculation of correlation coefficients. Negative correlations were noted between plasma angiotensin II levels and cardiac index ($r=-0.51$, $p<0.05$) as well as diastolic arterial pressure ($r=-0.70$, $p<0.001$), while positive relationships were observed with right heart pressures: mean pulmonary artery ($r=0.53$, $p<0.05$), pulmonary artery end-diastolic pressure ($r=0.58$, $p<0.01$), and right atrial pressure ($r=0.56$, $p<0.01$). Similar but generally weaker correlations between plasma renin activity, aldosterone and the above haemodynamic variables were observed (Table 8.3).

There was no relationship between plasma catecholamine levels and cardiac or hormonal function with the exception of ventricular filling pressures. Plasma norepinephrine and epinephrine correlated significantly with pulmonary artery end-diastolic pressure ($r=0.55$ and 0.56, $p<0.01$ respectively) and right atrial pressure ($r=0.62$, $p<0.01$ and $r=0.44$, $p<0.05$), but not with cardiac index, arterial pressure or heart rate. No clear cut relationship was found between calculated systemic vascular resistance and any of the hormone measurements, but it did correlate with plasma urea ($r=0.60$, $p<0.01$).

There were no close relationships between plasma ADH and any index of cardiac function.

TABLE 8.3: HORMONE - HAEMODYNAMIC RELATIONSHIPS

	CI	SAP	DAP	MAP	MPAP	PAEDP	RAP	HR	SVR
PRA	-0.10	-0.12	-0.45 *	-0.32	0.36	0.50 *	0.48 *	0.11	0.02
A II	-0.51 *	-0.23	-0.70 ‡	-0.53 *	0.53 *	0.58 †	0.56 †	-0.14	0.25
ALDO	-0.10	0.13	-0.48 *	-0.19	0.17	0.15	0.34	0.04	0.04
NOREPI	-0.19	-0.24	-0.05	-0.08	0.28	0.55 †	0.62 †	0.10	0.30
EPI	-0.07	-0.32	-0.18	-0.25	-0.32	0.56 †	0.44 *	0.12	0.13
CORT	0.12	-0.06	0.13	0.00	0.14	0.00	0.53 *	0.09	0.07
ADH	-0.26	-0.07	0.43	0.18	0.07	0.02	-0.02	-0.23	0.29
NA	-0.36	-0.52 *	-0.07	-0.33	0.17	0.29	0.08	0.22	0.35
K	0.07	-0.26	0.01	-0.14	-0.06	-0.09	-0.22	0.49 *	-0.12
CR	-0.32	-0.05	-0.41	-0.27	0.29	0.18	0.27	-0.09	0.26
UREA	-0.53 †	-0.06	-0.30	-0.18	0.16	0.33	0.32	-0.08	0.60 †
CR CL	0.39	0.02	0.41	0.24	-0.32	-0.26	-0.09	0.28	-0.25

* = $p<0.05$; † = $p<0.01$; ‡ = $p<0.001$. CI = cardiac index; SAP,DAP,& MAP = systolic, diastolic, and mean arterial pressure respectively; MPAP = mean pulmonary artery pressure; PAEDP = pulmonary artery end diastolic pressure; RAP = right atrial pressure; SVR = systemic vascular resistance. Plasma levels of renin activity, angiotensin II, aldosterone, norepinephrine, epinephrine, cortisol, antidiuretic hormone, sodium, potassium, and creatinine are denoted by the following symbols: PRA, AII, ALDO, NOREPI, EPI, CORT, ADH, NA, K, & CR. CR CL = creatinine clearance.

8.4 DISCUSSION:

Direct measurement of cardiac output and intra-cardiac pressures has become the time-honoured method for assessing the severity of cardiac dysfunction and the effects of therapeutic intervention (Braunwald, 1980). Following right heart and arterial catheterisation, control data are usually collected over a period of minutes to hours before the initiation of a new therapeutic regime. In a recent study performed in this unit (Maslowski et al, 1981a), a significant decline in right heart pressures, plasma epinephrine and cortisol levels (see fig 8.1 and 8.2) was observed during a 48 hour control period following cardiac catheterisation. These findings suggest that the stress of initial catheterisation adversely effects haemodynamic and hormonal parameters, and with bed rest, these recordings return to a true baseline. As a result of these observations, the protocol for subsequent investigations was altered so that catheters were inserted on the afternoon prior to, rather than on the morning of the first day of control measurements. I now report on the stability of these control measurements in these patients (n = 15).

Haemodynamic parameters did not alter over the two study days, apart from cardiac index which increased in relation to meals, a phenomenon documented many years ago (Grollman, 1929). Minor metabolic fluctuations were observed. Urine sodium output exceeded dietary intake throughout, while body weight was lower on the second day, even though oedema was not evident. Presumably this was due to the natriuresis of bedrest and adjustment to the constant dietary intake. Plasma renin activity and urine aldosterone levels were higher on the second day, while plasma epinephrine levels were slightly higher on the first day. Levine et al (1982b) have shown that the activity of the renin-angiotensin-aldosterone system remains constant over a three day period in ambulant patients with a stable clinical condition. However, the stress of cardiac catheterisation on the third day enhanced activity of the sympathetic nervous system as gauged by a rise in plasma epinephrine levels. This stress probably accounted for the higher levels in

this group of patients, as well as the greater fluctuations observed in patients 1 to 6.

A recent report (Thaulow et al, 1982) confirmed our impression that the stress of cardiac catheterisation significantly influences haemodynamic measurements for a considerable period of time. These investigators demonstrated a progressive fall in right heart pressures over an eighteen hour period following cardiac catheterisation. If drug intervention had been undertaken (with prazosin) during this period, these changes could have been attributed to a beneficial drug action. This highlights the difficulty in the interpretation of short-term investigations of the haemodynamic response to therapy where the effects of a changing baseline are all too often ignored. The present data would suggest that haemodynamic and hormonal indices adjust during the first twelve to eighteen hours after catheterisation and bed rest, then remain stable for a period of at least 48 hours. Stability over a longer period of time would be expected, thus an adequate baseline was probably established for the investigations described in Chapters 6 & 7.

Few studies use time-matched control data against which experimental results can be judged, thus they do not account for shifts in baseline produced by diurnal factors known to affect many of these indices. Despite this word of caution, little diurnal variation was observed, apart from cardiac index, plasma renin activity and cortisol. The patients with heart failure included in this study failed to show the usual diurnal pattern of change in arterial blood pressure reported for normal and hypertensive individuals (Millar-Craig et al, 1978a). More frequent recordings in nine patients confirmed these findings (fig 8.3), along with continuous 24 hour monitoring in three of these patients (see fig 6.8). To my knowledge, this phenomenon has not previously been reported. The reasons for this discrepancy are not apparent from the present study.

In contrast to the brisk response of the renin-angiotensin system to frusemide observed in individuals with normal cardiac function (Rosenthal et al, 1968; Hesse et al, 1975), I observed a blunted response to frusemide in nine patients on chronic therapy (fig 8.3) similar to the first dose effects of frusemide reported earlier from this unit (Ikram et al, 1980). Possible reasons for this blunted response include:

1. Augmented delivery of sodium chloride to the macula densa which may reduce renin secretion as it does in normal subjects who are sodium depleted (Judson & Helmer, 1971);

2. Possible suppression of renin release by digoxin (Antonello et al, 1976);

3. Lack of significant fall of right atrial pressure in our patients, which in normal individuals contributes to renin release (Kiowski and Julius, 1978).

Plasma aldosterone failed to show the significant diurnal variation reported by Sakamaki et al (1981). In their study, eight of eleven patients had mild heart failure (NYHA Class II) and were on little or no diuretic therapy. In patients with moderate to severe heart failure on diuretic therapy, activation of the renin-angiotensin system probably opposes and diminishes the effect of ACTH levels.

The results from this study clearly show that there are two major factors that determine the activity of the renin-angiotensin-aldosterone system in compensated heart failure:

1. Severity of cardiac disease;
2. Doses of frusemide therapy.

Plasma renin activity, plasma angiotensin II and aldosterone levels were greater with increasing severity of heart disease as judged by NYHA Functional Class (fig 8.4). As expected greater haemodynamic

abnormalities were found in the more severely afflicted groups. Cardiac index was lower while pulmonary artery pressures were higher in Class III and IV patients (fig 8.4). Furthermore, there was a close negative relationship between plasma angiotensin II (the major effector hormone of the renin system) and cardiac index, diastolic, and mean arterial pressure, while a close positive relationship was observed with right heart pressures. Such relationships were not seen with plasma norepinephrine, which is taken as a good index of "global" sympathetic function (Goldstein, 1981).

Elevations of plasma renin activity and aldosterone concentration have not been consistently observed in heart failure (Merril et al, 1946; Brown et al, 1970; Sanders & Melby, 1964; Wolff et al, 1959; Genest et al, 1968; Chonko et al, 1977; Kubo et al, 1980). These studies can be criticised for lack of clear definition of the clinical status of their patients, and failure to control other factors affecting this hormone system - body posture, diet and drug therapy (Levine et al, 1982b; Haber, 1969; Dzau et al, 1981; Meurer et al, 1972). Dzau et al (1981) have suggested that the system is activated following an acute diminution in cardiac function or increased metabolic demand, but returns to normal as plasma volume expands and patients enter a "compensated" state. From our data "compensation" would appear to be incomplete in Class III to IV patients as the renin-angiotensin system remains abnormally activated, albeit not to the same extent as during acute decompensation.

Diuretic therapy plays a major role in activating the renin-angiotensin-aldosterone system in heart failure. The relative contribution of frusemide dosage and the severity of myocardial dysfunction, however, could not be gleaned from our results. Knight et al (1979) demonstrated a close relationship between frusemide dose and plasma aldosterone levels. These data confirm the primacy of angiotensin II in controlling aldosterone secretion in heart failure under the conditions of study, relegating other secretagogues (ACTH and potassium) to relatively minor roles. The close correlation of plasma angiotensin II to haemodynamic

abnormalities in heart failure would tend to indicate that diuretic therapy may be a major factor in producing increased ventricular afterload and hyperaldosteronism. Acute haemodynamic improvement follows blockade of the formation of angiotensin II (see Chapter 6) and this appears to be greater in patients with greater activity of the renin-angiotensin-aldosterone system on higher doses of diuretics. Moreover, this effect appears to be sustained (see Chapter 10), in contrast to other vasodilators to which tolerance is often observed (Colucci et al, 1980a; Packer et al, 1981).

Dietary sodium intake did not appear to affect activation of the renin-angiotensin-aldosterone system greatly, as mean plasma renin activity and angiotensin II levels were similar in "low" and "normal" sodium intake groups, although plasma and urine aldosterone levels were definitely higher in the "low" intake group. Earlier work in heart failure patients is difficult to interpret, as Chonko et al (1977) found elevated plasma aldosterone levels despite sodium loading, while Sanders & Melby (1964) found no correlation between sodium balance and aldosterone excretion. In normal individuals and hypertensive patients, sodium restriction induces marked activation of the renin system (Haber, 1976). From the data presented here, this effect appears to be blunted in heart failure, presumably because cardiac dysfunction and diuretic therapy have a greater effect.

There was an inverse relationship between plasma sodium and plasma renin activity, although this was not as strong as others have reported (Levine et al, 1982a; Brown et al, 1970). This may be explained by the smaller range in plasma sodium concentration (130 - 141 mmol/l) in our patients. I also confirmed a relationship between plasma renin activity and urea and creatinine (Brown et al, 1970). These authors suggest several reasons for the above relationships:

1. A primary reduction in renal blood flow in heart failure may increase plasma renin activity, creatinine, and urea, while lowering plasma sodium;

2. Renin may alter intra-renal haemodynamics resulting in inappropriate concentration of urine, with an increase in plasma urea, and sodium;

3. Diuretic therapy promotes sodium loss, and stimulates renin secretion thus enhancing the relationship between these two parameters.

Compared to the renin-angiotensin system, sympathetic activity (as reflected by circulating catecholamines) was not strongly related to NYHA Functional class, frusemide dosage or haemodynamic parameters. Other workers have reported a better separation of plasma norepinephrine levels according to NYHA Class (Thomas & Marks, 1978), and significant relationships with haemodynamic parameters (Levine et al, 1982b; Kluger et al, 1982; Francis et al, 1980). In these studies, haemodynamic measurements were performed soon after cardiac catheterisation, thus their assessment is likely to have been affected to a greater extent by stress. The sympathetic nervous system is integrally involved with minute-to-minute regulation of the circulation, while the renin-angiotensin system is probably involved in longer-term regulation (Guyton, 1981). It is perhaps not surprising, then, that measurements performed well after cardiac catheterisation do not show the same strong association with sympathetic activity as do short-term studies. Undoubtedly, the results from the present study more truly represent long-term changes that occur in heart failure, and may well explain, in part, the dramatic long-term effectiveness of angiotensin converting enzyme inhibitors (see Chapter 10) compared with other vasodilators (eg. prazosin, hydrallazine) where tolerance to therapy often occurs (Colucci et al, 1980a; Packer et al, 1982).

Control of ADH secretion is multifactorial and complex (Robertson, 1977), the major routes and rate of clearance from plasma have yet to be clarified in cardiac failure. It is difficult to comment on the role of antidiuretic hormone in the patients in this study. Measurements were made at different times of the day

(1130 hr in eight patients and 0830 hr in six patients) while fluid intake was not strictly controlled. Levels of plasma antidiuretic hormone were generally within the range observed in healthy volunteers on an unrestricted diet and fluid intake. The data failed to show any close association of known or suspected stimuli with concurrent antidiuretic hormone levels. These include arterial pressure, left ventricular filling pressure, plasma sodium and angiotensin II levels. Interestingly, there was a significant association with frusemide dosage ($r = 0.55$, $n = 15$, $p < 0.05$). Elucidation of the role of antidiuretic hormone in heart failure will require further study with better control of fluid intake and blockade of antidiuretic hormone action and/or formation.

The grouping of such heterogenous disorders as ischaemic and dilated cardiomyopathy in a therapeutic trial causes some concern as the response to intervention may be affected by the underlying myocardial pathology. Under the conditions of our study, haemodynamic and hormonal indices could not be distinguished according to the aetiology of heart failure. Apparently the haemodynamic and neurohumoral changes are non-specific and secondary to impaired myocardial function, at least in the latter phases of cardiac failure. Furthermore, cardiac rhythm did not appear to influence activation of the renin-angiotensin-aldosterone system or the sympathetic nervous system, despite cardiac index and heart rate being lower, and ventricular filling pressures higher in the presence of atrial fibrillation.

8.5 CONCLUSION:

Cardiac catheterisation and bed rest appear to significantly influence cardiac function and hormone levels for a period of at least twelve hours. These changes seriously limit interpretation of short-term haemodynamic studies, especially with those investigating hormone-haemodynamic interactions in heart failure. Following this period of instability, cardiac function and hormone levels are relatively stable, more truly representing baseline levels. Having established such a baseline, the effects of therapeutic intervention on cardiac and hormone function may be more adequately assessed, especially as time-matched control recordings for any diurnal variation.

Activation of the renin-angiotensin-aldosterone system was largely dependent on frusemide dosage and severity of underlying myocardial dysfunction as judged by NYHA Functional Classification and haemodynamic parameters, while dietary sodium intake and plasma sodium played only a minor role. Judging by circulating catecholamines, the sympathetic nervous system was activated in some Class III and IV patients, but relationships with haemodynamic parameters were not as close as with plasma angiotensin II levels. This may explain, in part, the dramatic effectiveness of angiotensin converting enzyme inhibitors compared with other vasodilators (including postsynaptic alpha-1 antagonists - eg. prazosin) to which some patients become tolerant.

Activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system did not appear to be affected by underlying myocardial pathology or heart rhythm.

CHAPTER 9

BETA-BLOCKADE IN DILATED CARDIOMYOPATHY - IS IT BENEFICIAL ?

9.1 INTRODUCTION:

Since 1975 a Swedish centre has published a series of papers purporting to show that beta-blockade improves symptoms and survival in dilated (congestive) cardiomyopathy (Waagstein et al 1975, Swedberg et al 1979, 1980a, 1980b). The authors have claimed improvement in the clinical state, exercise capacity and ventricular function assessed by non-invasive methods. Furthermore, they claim that their patients' heart failure relapses on withdrawal of beta-blockade (Swedberg et al, 1980b).

This paradoxical form of therapy is completely contrary to our concepts of the role of the sympathetic nervous system and circulating catecholamines. Based on a substantial body of clinical and experimental data, the activation of the sympathetic nervous system (Chidsey et al, 1965; Braunwald, 1979) associated with a mild elevation of circulating catecholamines (Thomas and Marks, 1978) observed in cardiac failure is an important compensatory mechanism. Furthermore, blockade of this system by guanethidine (Gaffney and Braunwald, 1963) or propranolol (Epstein &Braunwald, 1966) results in greater impairment of cardiac function at rest or during exercise (Epstein et al, 1965).

All the Swedish studies were deficient in that they were neither controlled nor double-blind. Thus, the only rationale for beta-blockade at the present time is empirical observation. Whilst this is not unusual in therapeutics, it does require a highly critical evaluation of the adequacy of supporting evidence. The minimum requirement for acceptance of any new therapy is a positive result from a randomised controlled trial conducted in an adequate number of patients according to an appropriate protocol. The positive observations should be independently confirmed by one or more centres. In the absence of such

trials, the therapeutic value of this treatment remains to be proved.

The purpose of this study was to investigate the effects of oral beta-blockade in dilated cardiomyopathy by means of a controlled, cross-over, double-blind trial.

9.2 PATIENTS AND METHODS:

1. Patients:

Seventeen patients were studied, sixteen men and one woman with an age range of 30 to 62 years (mean 52 years). Table 9.1 gives the clinical details as well as other medications taken during the trial period, which were held constant throughout.

Congestive cardiomyopathy was diagnosed on the criteria of Goodwin and Oakley (1972). Coronary artery, pericardial, valvular, and congenital heart disease were excluded by prior right and left heart catheterisation, angiocardiography and selective coronary angiography. Secondary cardiomyopathies were excluded by appropriate tests and infiltrative cardiac muscle lesions by haemodynamic studies and endomyocardial biopsy.

All patients had had at least one episode of congestive cardiac failure resulting from cardiac muscle dysfunction. None of the patients had obstructive airways disease.

TABLE 9.1 CLINICAL DETAILS :

Patient number	Sex	Age	Possible Aetiology	NYHA Class	Rhythm	Other medications
1	M	43	Alc	II	AF	Warfarin
2	M	62	Alc	III	SR	Digoxin, Thyroxine
3	M	58	IP	III	AF	Digoxin, Thiazide
4	M	49	Alc	II	SR	Digoxin, Frusemide
5	M	62	Alc	III	AF	Digoxin, Frusemide
6	M	42	Alc	III	SR	Digoxin, Frusemide
7	M	30	IP	II	SR	Digoxin, Frusemide
8	M	60	Alc	II	AF	Digoxin, Frusemide
9	M	44	Alc	III	AF	Digoxin, Frusemide
10	M	41	Alc	III	SR	Digoxin, Frusemide
11	M	52	Alc	III	SR	Digoxin, Frusemide
12	F	55	IP	III	SR	Digoxin, Frusemide
13	M	61	IP	II	SR	Digoxin, Frusemide
14	M	57	Alc	II	AF	Digoxin
15	M	53	Alc	II	SR	Frusemide
16	M	64	IP	III	AF	Withdrawn from study
17	M	56	Alc	III	SR	Withdrawn from study

Alc = Alcohol ; IP = Idiopathic;
AF = Atrial Fibrillation;
SR = Sinus Rhythm.

2. Protocol:

At the start of the trial, the patients had a standard 6ft chest X-ray, an echocardiogram, and a familiarisation treadmill exercise test. They then entered a randomised double-blind crossover trial of one month's treatment with acebutolol ("Sectral") 200mg orally twice daily and placebo. Acebutolol was chosen because it has partial agonist activity and some cardioselectivity (Mason et al, 1978), thus it lies midway between the two groups of beta-blockers used in the Swedish Studies. The one month treatment period was chosen since most benefit was reported to occur early (Swedberg et al, 1980a). At the end of each treatment period they were re-investigated with a chest x-ray, echocardiogram and exercise test.

Echocardiograms were recorded on an 'Ekoline' 21 recorder (Smith-Kline Instruments). The standard technique described by Feigenbaum (1972) was employed for examination of the mitral and aortic valves and the sizing of the left atrium and ventricle. Much time and care was taken to get the antero-posterior diameter of the left ventricle just below the aortic root and through, or very close to both the anterior and posterior mitral leaflets. Three cardiac cycles were averaged when the patient was in sinus rhythm, while five cycles were averaged when the patient was in atrial fibrillation. The stroke volume was calculated from the end-diastolic and end-systolic volumes derived by the cube method (Pombo, Troy & Russel, 1971) and the cardiac output was estimated from the stroke volume and heart rate recorded during the procedure. For technical reasons four patients could not be studied adequately by echocardiography.

Progressive multi-stage, exercise testing was performed on a treadmill, Quinton Model 643, according to the "Bruce Protocol" (Bruce, Kusumi & Hosmer, 1973). The patients were exercised until they signalled that they could no longer continue. Electrocardiogram and heart rate were recorded on an Avionics "Exer Stress" Model 3000, and blood pressure measurements prior to, and

during the test were performed at one minute intervals with an Avionics "Pressurometer" Model 1905. Ventricular extrasystoles during exercise were assessed according to the modified Lown Grading System (Lown & Wolf, 1971).

On-line computer analysed breath-by-breath measurements of oxygen consumption (V_{O2}), carbon dioxide production (V_{CO2}) and ventilation (V_E) during exercise were performed on thirteen patients (see Chapter 3).

3. Statistical Analysis:

Statistical analysis was performed by Student's paired T-test when comparing the effect of acebutolol with that of placebo, and Student's T-test when comparing unpaired group means. An analysis of variance excluded significant order effect, but confirmed significant drug effects shown by paired T-test.

9.3 RESULTS:

1. Effect on Clinical State:

Of the fifteen patients who completed the study, none reported an improvement in symptoms and NYHA Functional Class was not altered. Two patients were withdrawn before completion of the trial:

1. Patient 16 died from pulmonary embolism and acute pulmonary oedema while on placebo;

2. Patient 17 experienced profound hypotension after the first dose of acebutolol, requiring inotropic support with isoprenaline. Challenge with lower doses of acebutolol also caused significant hypotension.

2. Effect on Ventricular Function: (Table 9.2)

Beta-blockade significantly increased cardiothoracic ratio. Echocardiography showed slight reductions in left ventricular systolic and diastolic diameter and volume, and left atrial size, while there was a slight rise in stroke volume and ejection fraction. None of these changes, however, were significant. The estimated cardiac output was significantly lower on beta-blockade largely due to the significant reduction in heart rate.

3. Effect on Exercise Performance: (Table 9.2)

The duration of exercise was significantly reduced ($p<0.01$), while resting and maximum heart rate and systolic blood pressure were very significantly reduced ($p<0.001$). There was a slight reduction in oxygen consumption, carbon dioxide production, and ventilation at maximum exercise, but none of these changes was statistically significant. There was no change in the anaerobic threshold when respiratory quotient (R) was compared with V_{O2}

TABLE 9.2 RADIOGRAPHIC, EXERCISE, AND ECHO DATA:

	Acebutolol	Placebo	n	p
Chest X-Ray:				
Cardiothoracic Ratio	0.55 + 0.07	0.51 ± 0.08	15	<0.01
Exercise data:				
Endurance Time (min)	6.53 + 3.90	7.33 + 3.75	15	<0.01
Resting HR	69.9 + 13.7	90.9 + 15.9	15	<0.001
Maximum HR	117 + 29	156 + 29	15	<0.001
Resting SBP (mm Hg)	128 + 13	140 + 17	15	<0.01
Maximum SBP (mm Hg)	173 + 30	204 + 32	15	<0.01
V_{O2} Max (l/min)	1.7 + 0.6	1.8 + 0.6	13	NS
V_{CO2} Max (l/min)	1.8 + 0.8	2.0 + 0.9	13	NS
R Max	1.1 + 0.2	1.1 + 0.2	13	NS
V_E Max (l/min)	56.7 + 24.5	61.8 + 23.8	13	NS
Echocardiographic data:				
SD (cm)	6.4 + 0.9	6.6 + 1.1	11	NS
SS (cm)	5.0 + 1.0	5.2 + 1.2	11	NS
Left atrial size (cm)	4.4 + 0.9	4.6 + 1.0	11	NS
LVEDV (cm^3)	223 + 61	233 + 73	11	NS
LVESV (cm^3)	125 + 54	140 + 68	11	NS
Ejection Fraction (%)	47 + 13	44 + 15	11	NS
Stroke Volume (cm^3)	98 + 23	93 + 33	11	NS
Cardiac Output (l/min)	6.2 + 1.4	7.4 + 2.0	11	<0.05

n = number of patients studied.

Results are expressed as mean ± standard deviation.

SD = diastolic ventricular diameter, SS = systolic vent. diameter,

R = respiratory quotient, NS = not significant (ie p>0.05).

4. Effect on Ventricular Extra-systoles During Exercise:

There was no significant difference in Lown Grading Score (results not shown) between placebo and active conditions using the Wilcoxon Matched Pairs Signed Ranks test ($p=0.20$).

5. Effect of Functional Class:

NYHA Class III patients were more severely afflicted than class II patients. Exercise capacity was lower (4.9 ± 3.1 min. compared to 10.0 ± 2.4 min., $p<0.01$), as was maximum oxygen consumption (16.8 ± 4.7 ml/Kg/min compared to 27.5 ± 4.7 ml/Kg/min, $p<0.005$) and maximum heart rate (138 ± 23 bt/min compared to 177 ± 18 bt/min, $p<0.005$). Cardiothoracic ratio, echocardiographic dimensions and ejection fraction also demonstrated greater impairment of cardiac function in Class III patients, however differences did not achieve conventional levels of statistical significance.

Acebutolol produced a greater reduction in exercise capacity in Class III patients (27% compared to 6% in Class II, $p<0.01$). Similarly, maximum heart rate was reduced to a greater extent (28% compared to 18%, $p<0.05$), as was the resting heart rate (24% compared to 18%, $p=0.07$). The effect of acebutolol on other parameters was not influenced by NYHA Functional Class.

6. Effect of Rhythm:

Comparing patients in sinus rhythm with those in atrial fibrillation (results not shown) for all parameters, there was no statistically significant difference between acebutolol and placebo, except that acebutolol produced a greater reduction in resting heart rate in patients with atrial fibrillation ($p<0.05$).

9.4 DISCUSSION:

Currently, the role of beta-blockade therapy in dilated cardiomyopathy remains controversial. The initial encouraging reports (Waagstein et al 1975, Swedberg et al 1980a, 1980b) have not been followed by independent confirmation by others or a controlled study by its originators. Anecdotal reports of benefit in small numbers of patients (Dwyer 1981, Alexander 1981) are counter-balanced by descriptions of serious haemodynamic complications in as few cases (Kohn, 1978; Hoffbrand, 1980; Breizis, Salnikowicz & Hasin, 1981).

In view of the importance of the sympathetic nervous system in stimulating the contractility of the normal myocardium, the activity of this system has also been studied extensively in patients with congestive heart failure. As outlined in Chapter 1, plasma norepinephrine provides an index of the activity of the sympathetic nervous system, at rest and during exercise, (Goldstein, 1981). During exercise, no change or very little increase in the norepinephrine concentration occurs in normal subjects, but much greater increases are seen in patients with congestive heart failure (Chidsey et al, 1962), presumably because of an increased activity of the sympathetic nervous system during exercise in these patients.

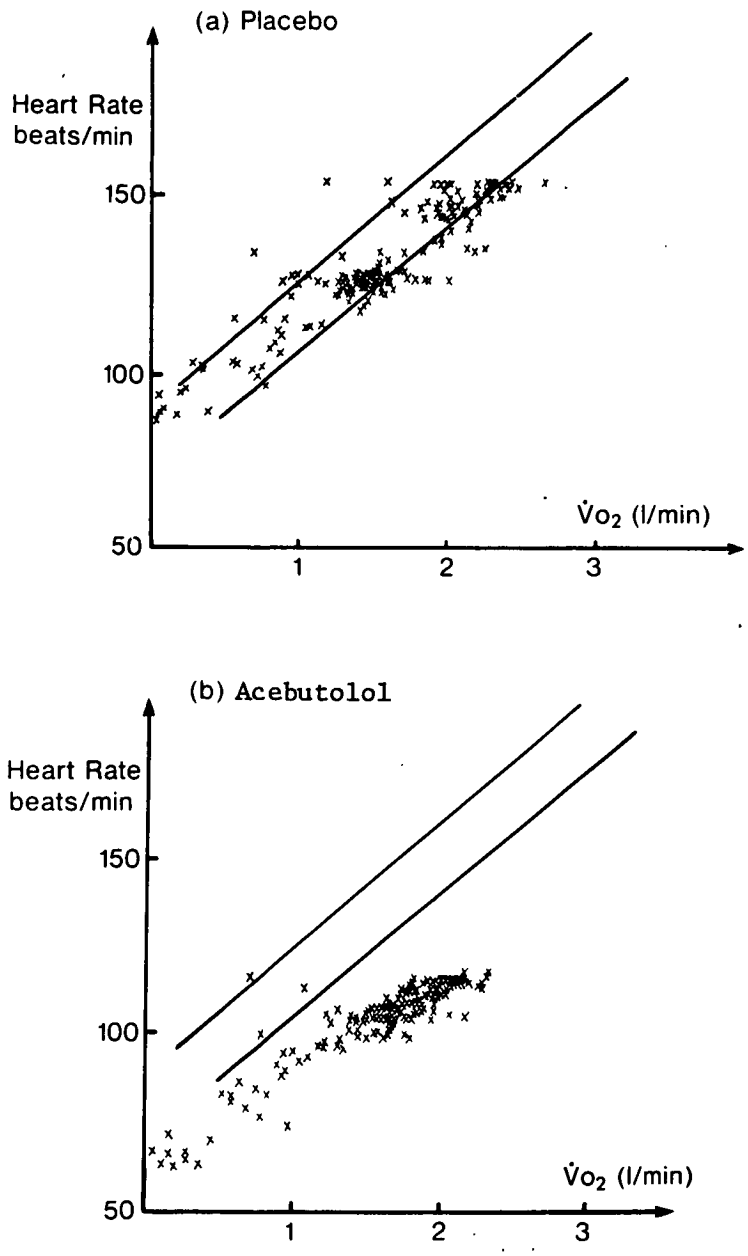
The importance of the increased activity of the sympathetic nervous system in maintaining ventricular contractility when the function of the myocardium is depressed is also shown by the effects of adrenergic blockade in patients with heart failure. Antiadrenergic drugs (guanethidine and propranolol) may cause sodium and water retention, as well as intensification of heart failure (Gaffney & Braunwald, 1963; Epstein & Braunwald, 1966). Haemodynamic deterioration and reduced exercise capacity have also been reported (Ikram et al, 1979; Taylor & Silke, 1981). The sympathetic nervous system plays an important compensatory role in heart failure and, until now, heart failure has been considered a major contraindication to the use of beta-blocking drugs (Taylor & Silke, 1981).

A healthy person responds to beta-blockade with a fall in resting heart rate and blood pressure (Lewis et al, 1973) and an increase in cardiac size (Chamberlain, 1966). The rise in heart rate and blood pressure in response to dynamic exercise is attenuated, leading to reduction of exercise capacity (Epstein et al, 1965). In patients with ischaemic heart disease and normal left ventricular function, beta-blockade diminishes myocardial oxygen consumption at any given level of activity, largely due to the reduction in heart rate (Epstein & Braunwald, 1966). The resultant elevation of anginal threshold (Armstrong et al, 1977) leads to enhanced exercise tolerance (Gianelly et al, 1969). In patients with ischaemic heart disease associated with depressed myocardial function, the detrimental effect of beta-blockade on ventricular function appears to over-ride any improvement in anginal threshold, thus exercise capacity is reduced (Taylor & Silke, 1981).

The present study failed to confirm the improvement in exercise performance reported by the Swedish workers. Moreover, exercise performance deteriorated to a greater extent in NYHA Class III patients, the very patients reported to derive most benefit from beta-blockade. Maximum heart rate was lower in Class III than in Class II patients, suggesting greater impairment of sympathetic drive to the myocardium in these patients (Goldstein et al, 1975). It was not surprising, then, that exercise performance was curtailed to a greater extent in Class III patients as they are likely to be more sensitive to beta-blockade.

Before beta-blockade, the response of heart rate and oxygen uptake to submaximal exercise was qualitatively normal in Class II and Class III patients, but following beta-blockade the response was depressed as illustrated in fig 9.1. This figure demonstrates that the oxygen pulse (V_{O2}/HR) was higher during beta-blockade, suggesting that cardiac output was maintained and stroke volume was higher at a given workload. The additional possibility of lowered mixed venous oxygen tension was not investigated. Furthermore, the curtailment of exercise was due to cardiac effects of beta-blockade (ie. on heart rate) and not due to the effect on airway resistance, since maximum oxygen consumption and ventilation were unchanged.

FIG 9.1



Graphical display of heart rate (HR) and oxygen consumption (V_{02}) measured on patient 15 during exercise: (A) on placebo; and (B) on acebutolol. Normal values are those used by Jones et al (1975). The boundaries represent $\pm$ standard deviation from the mean values at each level of oxygen consumption.

I found a significant fall in resting and post-exercise blood pressure (in one case necessitating withdrawal from the study). One might have expected this to be associated with a fall in vascular resistance. However, in ischaemic cardiomyopathy, beta-blockade reduces arterial pressure while vascular resistance remains high, presumably due to a greater fall in cardiac output (Taylor & Silke, 1981). No patient reported improvement in symptoms on beta-blockade, and NYHA functional class was unchanged in all patients. The absence of benefit in this study is unlikely to be due to failure of patient compliance since the resting heart rate and blood pressure were reduced after beta-blockade.

With regard to the effects of beta-blockade on ventricular function in dilated cardiomyopathy, the Swedish evidence for improved left ventricular function was based on a decrease in cardiac volume as judged by cardiothoracic ratio and echocardiographic measurements, an increase in echocardographically determined ejection fraction and diminished intensity of the third heart sound on phonocardiography. This improvement is contrary to findings of other studies on the effect of beta-blockade on ventricular function. In an earlier acute intravenous investigation reported from this unit (Ikram et al, 1979), beta-blockade produced further dilatation of the left ventricle, as assessed by left ventricular cineangiography. In particular, the end-systolic volume (which is indicative of contractile function) increased by 21%. Graber et al (1971) and Mason et al (1978), using thermal dilution and computer fluoroscopy of surgically implanted markers, had earlier shown greater dilatation after beta-blockade in dilated cardiomyopathy and transplanted hearts. The favourable reports from Sweden were concerned with chronic oral administration, thus extrapolation from the above short-term studies is difficult because the observed acute changes may not necessarily reflect long-term effects.

From the present study, however, oral beta-blockade produces further cardiac enlargement in dilated cardiomyopathy and does not corroborate the findings of the Swedish investigators. Echocardiography clearly demonstrated the increase in left ventricular volume, which is the hallmark of this disorder, but was unable to detect any significant decline in ventricular volume or improvement in ejection fraction with

beta-blockade. M-mode echocardiographic assessment of left ventricular function may be very unreliable in such patients as they often have gross dilatation, minimal wall excursion, as well as regional wall motion abnormalities and functional mitral incompetence. Any "improvement" in ventricular function, as assessed by ejection fraction, may result from increased mitral regurgitation or reduced ventricular afterload due to a fall in arterial blood pressure.

Another double-blind placebo-controlled study using metoprolol in a one-by-one month crossover design has subsequently been reported (Currie et al, 1982). Nine patients who filled the clinical criteria for dilated cardiomyopathy, all in NYHA Class III with ejection fraction of less than 35% (determined by echocardiography) were evaluated by Swan-Ganz catheterisation, supine exercise testing and radionuclide angiography. Four patients felt better on metoprolol, while five felt better on placebo. Ejection fraction, cardiac index, pulmonary end-diastolic pressure and exercise performance were not altered. In this study, two patients were subsequently found to have severe three vessel coronary artery disease demonstrated by coronary angiography, highlighting the difficulty in clinically differentiating ischaemic cardiomyopathy from idiopathic dilated cardiomyopathy. It should be noted that coronary angiography was not performed routinely on the patients included in the Swedish studies.

There has been much speculation on how beta-blockade may be beneficial (Taylor & Silke, 1981). Detrimental effects of catecholamines on the failing myocardium have been postulated to cause cardiac dysrhythmias or myocardial damage similar to those seen occasionally in patients with phaeochromocytoma (Waagstein et al, 1975). Elevated levels of plasma catecholamines are encountered in heart failure irrespective of aetiology (Thomas & Marks, 1978), are similar to levels seen in patients with ischaemic cardiomyopathy (see Chapter 8), and are nowhere near the levels seen in phaeochromocytoma. Furthermore, Amorin et al (1981) were not able to demonstrate sympathetic overactivity in patients with early dilated cardiomyopathy, investigated before the onset of circulatory congestion. Suppression of renin levels by beta-blockade (Davies et al, 1977) has also been postulated to be

beneficial. Neither the Swedish workers nor I investigated the effects of beta-blockade on the renin-angiotensin-aldosterone system, but I did investigate the effect of beta-1 adrenoceptor stimulation on this system in another study (Chapter 7). In this study, I found that prenalterol stimulated the renin-angiotensin-aldosterone system, but in the short-term this did not appear to effect the direct action of the drug on the myocardium. Although it is difficult to extrapolate to long-term effects, the direct suppression of myocardial function by beta-blocking agents probably overrides any beneficial effect produced by reduction of renin release in heart failure.

The effect of beta-blockade on survival in dilated cardiomyopathy was not investigated in this study, but the Swedish findings (Swedberg et al , 1979) deserve some comment in this discussion. They report improved survival in 24 patients treated with beta-blockers compared with an historical control group. The pitfalls of using historical, as opposed to concurrent, randomised controls has been documented recently (Sacks et al, 1982). The positive outcome of trials using historical controls depends overwhelmingly on the historical control group doing significantly worse than randomised controls for the same therapy. Furthermore, the use of historical controls irrevocably biases the study in favour of the new therapy. If the Swedish control group is examined in this light, the 10% three-year survival in the control group is very low when compared to three-year survival of 52, 75 and 50% reported in three large series from the Mayo Clinic (104 cases), Georgetown University (115 cases) and the Hammersmith Hospital (74 cases) (Fuster et al, 1981; Segal et al, 1978; Goodwin, 1970 respectively). It is very likely that if the Swedish researchers had used randomised controls, their positive conclusion may have been a negative one. At the very least, the evidence is inconclusive on the point of survival.

9.5 CONCLUSION:

To date the effect of long-term beta-blockade in dilated cardiomyopathy has only been evaluated by two double-blind studies, both of which do not support a beneficial effect of these drugs. Whilst beta-blockade was surprisingly well tolerated, there are a number of case reports of severe cardiac failure and hypotension, hence, beta-blockade is not entirely benign in this condition. Dilated cardiomyopathy is not a homogeneous entity, so there may be small subsets of patients who will benefit from beta-blockade. Until the matter is resolved by randomised double-blind study in adequate numbers of patients, routine administration of beta-blocking agents in dilated cardiomyopathy cannot be recommended.

CHAPTER 10

WITHDRAWAL OF LONG-TERM CAPTOPRIL THERAPY FOR HEART FAILURE: A ONE MONTH CONTROLLED, DOUBLE-BLIND STUDY

10.1 INTRODUCTION:

To date, the sustained effectiveness of vasodilators in the long-term management of heart failure remains in doubt (Colucci et al, 1980a; Packer et al 1978,1982). In the case of angiotensin converting enzyme inhibitors, available data for long-term effectiveness consists of uncontrolled studies lasting less than six months where neither the patient nor the observer were blinded (Romankiewicz et al, 1983). This issue must remain in doubt until confirmed by a double-blind placebo controlled trial.

The sustained effectiveness of other vasodilators has been inferred from studies which demonstrated acute haemodynamic rebound following cessation of treatment (Packer et al, 1979; Black & Mehla, 1979; Hanley et al, 1980). Such deterioration in cardiac function was not observed after withdrawal of long-term captopril therapy for four days (Maslowski et al, 1981b). This may be interpreted as showing lack of long-term efficacy, or alternatively, four days may have been insufficient time for deterioration to occur. In this chapter, I report the effect of one month, double-blind withdrawal of long-term captopril therapy on cardiac and respiratory function, exercise performance and plasma electrolytes in ten patients with heart failure.

10.2 PATIENTS AND METHODS:

1. Patients:

The study population (Table 10.1) comprised ten patients aged 49 to 74 years with heart failure due to ischaemic heart disease (n = 8) or dilated cardiomyopathy (n = 2). They had been severely disabled (NYHA Class III or IV) before the addition of captopril to digoxin and frusemide therapy. Captopril induced a pronounced clinical improvement (Table 10.1) and at the time of the present study, all but three were in NYHA Class II after a mean treatment period of 12.5 months (range 4 to 25 months). Following improvement with captopril, frusemide therapy was withdrawn in patient 9 without clinical deterioration. Left ventricular function was quite severely depressed as indicated by a mean ejection fraction of 26.5% (range 12 to 40%). For at least one month prior to investigation clinical state and drug therapy were stable. Medications were continued unchanged throughout the period of investigation, digoxin being administered at a dose of 0.0625 mg to 0.25 mg daily, while frusemide therapy is documented in Table 10.1.

2. Protocol:

The protocol was approved by the Hospital's Ethical Committee, and all patients gave informed, written consent. The study entailed random, double-blind withdrawal of long-term captopril therapy for a period of one month. Patients were allocated randomly to placebo and captopril groups according to a predetermined scheme drawn up by the Squibb Company, which was not disclosed to the investigators. The company also provided placebo tablets of identical shape, size, colour, and taste. All patients continued on their usual dose schedule. At the beginning and end of the period of study, cardiac and respiratory function were assessed at rest and during exercise. Clinical state was assessed weekly, and I was available at all times if the patient's condition deteriorated suddenly.

TABLE 10.1: CLINICAL DETAILS

No.	Group	Age	Sex	Rhythm	Aet	Initial Response	Treatment Period(mo)	Daily Dose(mg)	Frusemide Dose (mg)
1	C	51	M	SR	DCM	IV →III	9	75	750
2	P	70	M	SR	IHD	IV →III	15	150	250
3	P	58	M	SR	IHD	III→ II	4	75	40
4	C	56	M	SR	IHD	III→ II	8	75	120
5†	P	74	F	AF	IHD	IV →III	18	150	1000
6†	C	56	M	SR	IHD	IV → II	23	150	750
7†	C	66	M	AF	IHD	III→ II	25	75	250
8†	P	52	M	SR	DCM	III→ II	8	75	80
9†	P	49	M	SR	IHD	III→ II	11	75	0
10†	C	59	M	SR	IHD	III→ II	5	100	40

The trial groups that patients were randomly allocated to are denoted by P = placebo group, and C = control group who remained on captopril therapy. SR = sinus rhythm, AF = atrial fibrillation, IHD = ischaemic heart disease, DCM = dilated cardiomyopathy. † = LVEF determined with the "Nuclear Stethoscope" at the beginning and end of the trial period (other studies were performed by Gamma Camera).

At the weekly clinic visits, patients were questioned closely for symptomatic changes. NYHA Class was assessed, and physical examination performed. Blood samples were taken for measurement of haematological and biochemical parameters. At the beginning and the end of the study, urine was collected for a 24 hour period to measure creatinine clearance. Computer-aided spirometry (see below) and radionuclide left ventricular ejection fraction were also performed at these times.

Invasive haemodynamics at rest and during exercise were assessed twice, at the beginning and the end of the study. At 0800 hr on each day of invasive investigation, a Swan-Ganz catheter was inserted via a brachial or subclavian vein for measurement of right heart pressures and cardiac output in triplicate by thermodilution technique. A radial or brachial artery cannula was inserted in the same arm for measurement of arterial pressure and blood sampling. As each invasive study was relatively brief, the risk of complications from distal migration of the tip of the Swan-Ganz catheter were minimal so pulmonary capillary wedge pressure was measured in every case. Captopril was administered, in the patients' usual dose, at 0700 hrs while diuretic therapy was withheld on the day of invasive investigation.

Baseline resting haemodynamic recordings were performed in the supine position at 1230 and 1245 hr (four hours after insertion of catheters). If recordings were stable, a further dose of captopril (or placebo on the second study day) was administered at 1300 hr, and haemodynamic recordings were repeated at 1500 hr. Patients were then transferred to the exercise room, seated on a bicycle ergometer (Elma-Schonander Ergometer EM 369), with the catheterised arm being supported at the level of the left atrium. On-line breath-by-breath measurements of oxygen consumption, carbon dioxide production and ventilation were performed. Instantaneous gas concentrations were measured with a respiratory mass spectrometer (Perkin-Elmer MGA 1100), a Fleisch pneumotachograph, and data processing was performed with a Digital PDP 11-10 computer, using software similar to that used by Beaver et al (1973).

After a suitable period of adjustment and when graphical display of oxygen consumption was stable, haemodynamic measurements were performed in duplicate, three minutes apart. The patients then commenced graded exercise with three minute stages of incremental workloads (50 - 150 kpm/min). These steps were predetermined from a familiarisation exercise test performed less than a week prior to entering the study to ensure that each patient exercised for approximately ten to twelve minutes. After two minutes of each stage of exercise, haemodynamic measurements were performed and blood was drawn for arterial lactate as well as arterial and venous haemoglobin oxygen saturation (Instrumentation Lab Inc Co-oximeter IL 182). Cardiac output during exercise was determined by Fick method. Each patient exercised for as long as he could before terminating, at which time haemodynamics and blood sampling were again repeated. Anaerobic threshold (Weber et al, 1982b) was achieved in all but one patient.

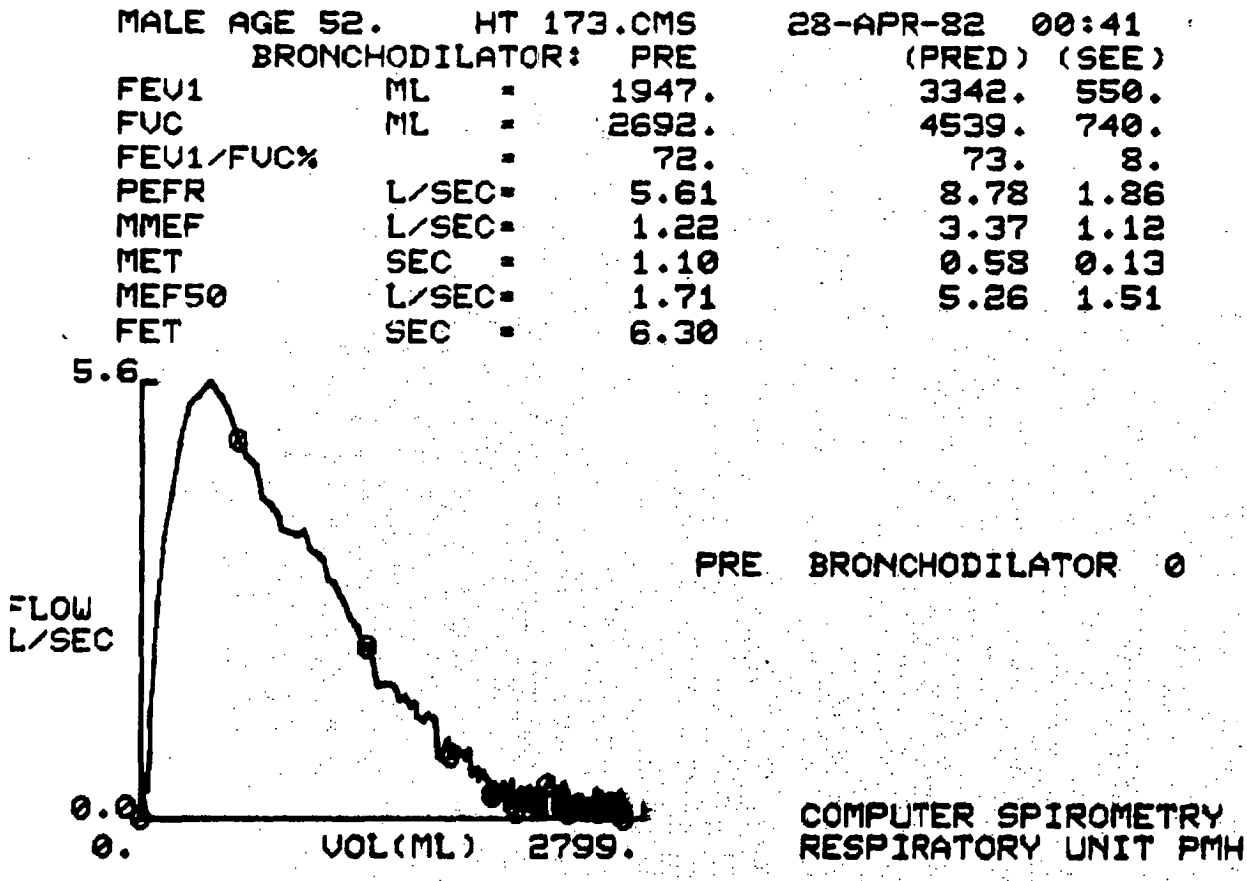
3. Statistics:

Statistical analysis was performed by Student's paired T-test when comparing results within each group. Differences between each group were analysed by Student's T-test. Results are expressed as mean $\pm$ standard error of the mean (SEM) unless stated otherwise.

4. Computer-assisted Spirometry:

Spirometry was performed on an Ohio 840 Dry Rolling Seal Spirometer thirty minutes after the exercise test. Patients inspired maximally, then forced expiration was performed into the spirometer. Interactive graphics (using a Digital PDP 11-10 Computer and a Tektronix 4012 Graphics Terminal) provided immediate analysis and display of the data. Corrections for ambient temperaure and barometric pressure were made automatically. Immediate display allowed recognition of a poorly performed test, so that the test could be repeated as required. Normal values, determined from reported regression equations (Cherniack & Raber, 1972), were also displayed. An example of a computer generated output is shown in Fig 10.1.

Figure 10.1: Computer-Assisted Spirometry



Flow-volume curve during forced expiration

FEV = forced expiratory volume in 1 second

FVC = forced vital capacity

PEFR = peak expiratory flow rate

10.3 RESULTS:

1. The Captopril Group:

Despite random allocation to placebo and captopril groups, some significant differences between the groups were encountered. Haemodynamic abnormalities were greater in the captopril group. Cardiac index was lower (2.03 ± 0.11 l/min/m^2 compared to 3.32 ± 0.38 l/min/m^2 in the placebo group, $p<0.05$) while mean pulmonary artery pressure (42.0 ± 3.8 mm Hg v. 21.8 ± 2.0 mm Hg, $p<0.01$) and pulmonary capillary wedge pressure (28.8 ± 2.2 v. 13.4 ± 1.6 mm Hg, $p<0.01$) were higher. Arterial pressure and right atrial pressure were also higher in the captopril group, but the differences were not significant. Despite these differences in resting haemodynamics, maximum oxygen consumption was similar in both groups.

After one month, haemodynamics in the captopril group tended to improve (Table 10.2) with falls in arterial pressure, right heart pressures and heart rate. These changes did not reach conventional levels of statistical significance, largely due to the smaller number of patients in this group, as one patient (No 6) in the captopril group had to be withdrawn from the study before it was completed. He developed acute lobar pneumonia complicated by acute on chronic renal failure three weeks after the first investigation. Consequently, his data have been excluded from most analyses, apart from the analysis of the effect of a single dose of captopril while on chronic therapy.

2. Clinical Findings in the Placebo Group:

Three significant clinical events occurred in the five patients in whom captopril was withdrawn:

1. Patient 2 complained of increasing dyspnoea over the first two weeks of the study, and as a result of this he asked to be withdrawn from the study. Repeat invasive investigations

were performed on the fourteenth day of the protocol, before the code was broken. Captopril was then recommenced with subsequent clinical improvement.

2. Patient 8 deteriorated from NYHA Class II to III, however he was happy to complete the protocol, and he improved when captopril was re-introduced.

3. Patient 5 complained of weakness and palpitations after ten days. On examination, she was pale and sweaty, while her blood pressure and heart rate were higher. Plasma potassium had fallen from 3.8 mmol/l to 2.5 mmol/l necessitating additional potassium supplementation. Symptoms of heart failure had not changed, so the treatment code was not broken, and the patient continued the trial. Plasma potassium had increased to 3.3 mmol/l by the time of second study.

Overall, cuff blood pressure increased significantly in the placebo group, however changes were not as dramatic as those measured by arterial cannulation, presumably because clinic times could not be standardised to a uniform time after the last dose of captopril. Body weight increased slightly from 68.8 $\pm$ 16.2 Kg to 69.4 $\pm$ 16.2 Kg, while resting radionuclide ejection fraction declined from 27 $\pm$ 6% to 26 $\pm$ 5%, neither change being significant.

3. Biochemical changes:

Plasma potassium tended to fall in those patients withdrawn from captopril, with the greatest fall occurring in patient 5 who was taking the largest dose of frusemide (1000 mg). No significant alterations in plasma sodium, urea, creatinine or creatinine clearance were observed. A fall in haemoglobin in the placebo group (14.5 $\pm$ 1.1 g/dl to 13.8 $\pm$ 1.3 g/dl), although small, did reach levels of statistical significance. No such changes were seen in the captopril group.

4. Resting Haemodynamics:

1. Effect of single dose of captopril while on chronic therapy:

At the time of the first study all ten patients were receiving captopril therapy. Resting haemodynamics were recorded two hours after a dose of captopril (1500 hr), measurements having already been performed at 1300 hr, six hours after the preceding dose taken at 0700 hr. Comparing the 1300 and 1500 hr results, the only parameter to show significant changes (Table 10.3) was arterial pressure. For this reason, results at each measurement time were combined, and daily means on the first and second study compared.

2. Effect of Captopril Withdrawal:

When haemodynamics were reassessed one month after cessation of long-term captopril therapy (Placebo group - Table 10.2), mean arterial pressure had increased from 80 $\pm$ 8 mm Hg to 96 $\pm$ 9 mm Hg ($p<0.05$), left ventricular filling pressure had risen from 13.4 $\pm$ 1.6 mm Hg to 17.8 $\pm$ 1.9 mm Hg ($p<0.05$), while right atrial pressure was higher (6.8 $\pm$ 2.0 mm Hg to 9.8 $\pm$ 1.3 mm Hg, $p<0.05$). Cardiac index declined while ventricular rate and mean pulmonary artery pressure rose slightly, but these changes were not statistically significant.

Comparison with the captopril group was hampered by significant differences between the two groups at entry, and the small number of patients in each group. Nevertheless, the mean individual differences in arterial pressure and pulmonary capillary wedge pressure were significantly different when analysed by Student's T-test ($p<0.05$).

TABLE 10.2: RESTING HAEMODYNAMICS AND SPIROMETRY:

	Placebo Group (n=5)		Captopril Group (n=4)	
	Study 1	Study 2	Study 1	Study 2
Cardiac Index ($l/min/m^2$)	3.32 + ±0.38	3.11 ±0.54	2.03 ±0.11	2.13 ±0.11
Syst Art Press (mm Hg)	125 ±14	142 * ±17	135 ±19	120 ±10
Diast Art Press (mm Hg)	61 ±3	74 * ±5	76 ±8	67 ±4
Mean Art Press (mm Hg)	80 ±8	96 * ±9	96 ±11	84 ±5
Mean Pulm Art Pr (mm Hg)	21.8 ++ ±2.0	25.4 ±4.0	42.0 ±3.8	30.5 ±4.9
PCWP (mm Hg)	13.4 ++ ±1.6	17.8 * ±1.9	28.8 ±2.2	18.5 ±4.4
Right Atrial Press (mm Hg)	6.8 ±2.0	9.8 * ±1.3	10.0 ±0.8	6.5 ±2.6
Ventricular Rate (bt/min)	78 ±7	85 ±12	78 ±8	74 ±3
FVC (l)	3.21 ±0.57	3.01 * ±0.57	3.65 ±0.18	3.96 ±0.33
$FEV_{1\ sec}$ (l)	2.18 ±0.33	2.07 ±0.31	2.53 ±0.36	2.78 ±0.36
FEV_1/FVC Ratio (%)	68.6 ±3.1	70.6 ±3.6	68.8 ±6.5	70.0 ±5.7
Pk Expir Flow Rate (l/min)	5.54 ±0.90	5.76 ±0.87	8.10 ±1.80	8.83 ±1.50

Mean ± SEM. PCWP = pulmonary capillary wedge pressure.
FVC = forced vital capacity. FEV = forced expiratory volume.
Significant differences between placebo and captopril groups on study day 1 are indicated by + = $p<0.05$, ++ = $p<0.01$, while significant difference between the two study days is indicated by * = $p<0.05$.

TABLE 10.3:

EFFECT OF A SINGLE DOSE OF CAPTOPRIL WHILE ON CHRONIC THERAPY

Time post dose (hr.)	6 (1300)	2 (1500)	Significance
Cardiac Index ($l/min/m^2$)	2.88 $\pm$0.30	2.93 $\pm$0.37	NS
Ventricular Rate (bt/min)	79 $\pm$4	79 $\pm$5	NS
Syst Arterial Pressure (mm Hg)	141 $\pm$12	127 $\pm$11	<0.01
Diast Arterial Pressure (mm Hg)	74 $\pm$5	67 $\pm$6	<0.05
Mean Arterial Pressure (mm Hg)	95 $\pm$6	88 $\pm$8	<0.05
Mean Pulmonary Art Press (mm Hg)	28 $\pm$4	25 $\pm$3	NS
Pulm Cap Wedge Pressure (mm Hg)	18 $\pm$3	17 $\pm$2	NS
Right Atrial Pressure (mm Hg)	7 $\pm$1	8 $\pm$1	NS
Systemic Vascular Resist ($dyne-sec-cm^{-5}$)	1408 $\pm$147	1379 $\pm$221	NS

Haemodynamic measurements in 1o patients (mean $\pm$ SEM) 2 hours (1500) after a dose of captopril, compared to measurements 6 hours after the previous dose.

5. Exercise Capacity:

In those patients in whom captopril was withdrawn, exercise duration declined from 13.5 $\pm$ 3.1 min to 11.4 $\pm$ 3.0 min ($p<0.05$), while in the captopril group, exercise duration was not altered (9.8 $\pm$ 1.5 min compared to 9.8 $\pm$ 0.5 min). Haemodynamics at maximal (table 10.4) and submaximal exercise (results not shown) were not significantly different in either group of patients.

6. Respiratory Function:

Forced vital capacity declined ($p<0.05$) in the group in whom captopril was withdrawn, but indices of upper airway resistance remained unchanged (Table 10.4). At peak exercise, oxygen consumption declined from 1.28 $\pm$ 0.35 to 1.12 $\pm$ 0.29 l/min, carbon dioxide production declined from 1.42 $\pm$ 0.46 to 1.33 $\pm$ 0.36 l/min, however neither change achieved conventional levels of statistical significance. Respiratory quotient and maximum ventilation were unchanged, as was oxygen extraction (Table 10.4). Arterial lactate at maximum exercise increased significantly in the captopril group ($p<0.05$) but declined in the placebo group, although this change was not significant. Comparisons of mean individual differences between each group, however, did show that trends were significantly different ($p<0.01$).

TABLE 10.4: HAEMODYNAMIC AND RESPIRATORY DATA AT MAX EXERCISE:

	Placebo Group		Captopril Group	
	Study 1	Study 2	Study 1	Study 2
Exercise Duration (min)	13.5 ±3.1	11.4 * ±3.0	9.8 ±1.5	9.8 ±0.5
Cardiac Index ($l/min/m^2$)	6.7 ±1.4	6.9 ±1.8	4.7 ±0.3	4.7 ±0.5
Ventricular Rate (bt/min)	139 ±6	134 ±8	141 ±17	136 ±18
Syst Art Press (mm Hg)	176 ±17	161 ±18	167 ±25	165 ±16
Diast Art Press (mm Hg)	84 ±3	86 ±6	79 ±10	82 ±3
Mean Art Press (mm Hg)	116 ±6	111 ±9	107 ±14	107 ±5
Mean PA Press (mm Hg)	37 ±7	34 ±7	56 ±8	45 ±6
V_{O2} (l/min)	1.24 ±0.35	1.12 ±0.29	1.26 ±0.15	1.24 ±0.17
V_{CO2} (l/min)	1.42 ±0.46	1.33 ±0.36	1.47 ±0.18	1.50 ±0.21
Ventilation (l/min)	43.8 ±13.0	44.6 ±11.0	53.0 ±3.3	54.3 ±4.9
Art Lactate (mmol/l)	5.4 ±1.8	4.3 ±1.3	4.6 ±1.5	5.6 * ±1.4

Mean ± SEM. V_{O2} = oxygen consumption. V_{CO2} = carbon dioxide production. For each group, significant differences between the two study days are shown by * = $p<0.05$.

10.4 DISCUSSION:

Exacerbation of heart failure may follow the abrupt withdrawal of vasodilator therapy (Packer et al, 1979; Black & Mehla, 1979; Hanley et al, 1980). These authors interpreted the observed changes as evidence for continuing effectiveness of vasodilator therapy. Such haemodynamic deterioration was not observed after cessation of captopril therapy for four days (Maslowski et al, 1981b). This might be taken to suggest that the drug has little or no effect in the long-term or, alternatively, that four days may be insufficient time for deterioration of cardiac function. In this study, I investigated the effects of ceasing captopril therapy for one month; the placebo controlled double-blind, protocol being chosen to facilitate the interpretation of results.

None of the patients in the captopril group exhibited a change in clinical status, although one patient had to be withdrawn because of an incidental illness. Significant clinical events occurred in three of five patients in whom captopril was withdrawn. The clinical state deteriorated considerably in two patients, with one patient shifting from NYHA Functional Class II to III and the other patient (already in Class III) asking to be removed from the study, because of increasing dyspnoea two weeks after commencing placebo medication. Potentially serious hypokalaemia developed over a period of ten days in patient 5. Overall, a fall in plasma potassium was noted (Table 10.2), but did not achieve levels of statistical significance. These effects are not surprising since initiation of therapy with converting enzyme inhibitors induces a positive cumulative potassium balance and a minor rise in plasma potassium (see Chapter 6) due, in part, to a fall in plasma aldosterone. In the absence of converting enzyme inhibition, plasma aldosterone levels in heart failure correlate closely with the dose of frusemide therapy (Chapter 8). Thus, the rise in plasma aldosterone attendant upon withdrawal of converting enzyme inhibition is likely to be greater in those patients on larger frusemide doses, such as patient 5 who required 1,000 mg daily.

The deterioration in clinical state was associated with an overall decline in left ventricular function as judged by resting haemodynamic parameters, whereas there was a tendency for improvement in the captopril group. Arterial pressure rose significantly, but resting cardiac output was sustained by a rise in filling pressures which probably induced greater pulmonary congestion and thus, a decline in forced vital capacity. It would appear that haemodynamic deterioration occurs gradually after the cessation of captopril therapy. In an earlier study from this unit (Maslowski et al, 1981b), haemodynamic or clinical deterioration did not occur during a four day period of withdrawal of long-term captopril therapy. Arterial pressure rose as a consequence of the rise in plasma angiotensin II, although greater activation of the sympathetic nervous system (as judged by the rise in plasma norepinephrine) may have contributed. Heart rate also rose significantly, correlating with rises in plasma angiotensin II and norepinephrine, but cardiac output and right heart pressures remained unaltered. Sodium retention or potassium depletion did not occur in this study, but the rise in plasma and urine aldosterone levels suggested that these changes may have developed had the period of withdrawal been longer. In the present study, sodium and water retention did not appear to be a major problem, as body weight did not rise significantly.

As mentioned earlier, rebound haemodynamic changes occur rapidly following the withdrawal of other vasodilators (Packer et al, 1979; Black & Mehta, 1979; Hanley et al, 1980). The haemodynamic response to vasodilator therapy results from two counteracting forces (Packer et al, 1981):

1. Direct peripheral vasodilating effects of the drug;

2. Secondary activation of counterposing mechanisms which cause peripheral vasoconstriction and tachycardia.

The second factor is perhaps largely responsible for the rebound haemodynamic changes induced by withdrawal of therapy, and has also been incriminated in the development of tolerance to these agents

(Colucci et al, 1980; Packer et al, 1982). As acute rebound was not observed following captopril withdrawal, the gradual deterioration appeared to be largely due to withdrawal of direct effects of the drug. Thus counterposing mechanisms reducing the effect of agents such as captopril do not appear to be great, and this may well contribute to the sustained effectiveness of this form of therapy.

In open trials, captopril therapy has been shown to improve exercise capacity in patients with severe heart failure (reviewed by Romankiewicz et al, 1982). In one study, single-blind withdrawal of therapy for two weeks resulted in a significant decline in exercise capacity (Cowley et al, 1982). The reasons for improved exercise capacity remain uncertain at the present time, but may be due to decreased pulmonary congestion or improved skeletal muscle perfusion during exercise which delays conversion to anaerobic metabolism. From the small numbers of patients that I studied, firm conclusions cannot be drawn. I found that captopril withdrawal produced a significant decline in exercise duration associated with a possible fall in maximum oxygen consumption and carbon dioxide production. Haemodynamic measurements did not appear to be different at submaximal or maximal levels of exercise, however, movement artifacts increased the error of measurement. The changes in arterial lactate are difficult to interpret with any certainty.

10.5 Conclusion:

Withdrawal of long-term captopril therapy may result in serious hypokalaemia, especially in those patients on large doses of diuretic therapy. An acute rebound haemodynamic response has not been observed, thus neurohumoral factors that counteract effects of many vasodilators are not greatly activated. Haemodynamic deterioration does occur gradually and is associated with an increase in symptoms and decline in exercise performance. These data indicate that captopril has a pronounced and sustained haemodynamic effect in patients with severe cardiac failure, which is reversed after temporary withdrawal of the drug.

CHAPTER 11

CONCLUSIONS

"No scientific investigation can be final, it merely represents the most probable conclusion which can be drawn from the data at the disposal of the writer. A wider range of facts, or more refined analysis, experiment and observation will lead to new formulae and new theories. This is the essence of scientific progress."

Karl Pearson (1898).

Although a large number of points have been discussed in the preceding chapters, only what appear to be the major findings will be summarised here. In the first three studies (Chapters 6, 7 and 8), investigations were performed under standard conditions of sodium and potassium balance and body posture, while usual digoxin and frusemide therapy remained constant. Measurements performed under control conditions and following therapeutic intervention allowed accurate interpretation of hormone levels and their relationships to haemodynamic abnormalities, as well as interpretation of the effects of therapeutic intervention.

For a period of at least twelve hours after cardiac catheterisation, haemodynamic and hormone parameters vary significantly. After this period of instability, a relatively stable baseline is achieved and remains that way for at least a further 48 hours. It is at this time that haemodynamic-hormone inter-relationships may be more accurately assessed, unrelated to the stress of catheterisation - these effects are all too often ignored, especially in short-term studies investigating therapeutic intervention. Study protocols that include an

adequate period of stabilisation and control measurements, such as those studies outlined in Chapters 6 & 7, allow greater accuracy in the assessment of the effects of new forms of therapy.

Activation of the renin-angiotensin-aldosterone and sympathetic nervous systems at rest was most evident in those patients with severe heart failure, on higher doses of frusemide. There was a close correlation between levels of angiotensin II and plasma renin activity with haemodynamic abnormalities of heart failure - reduced cardiac index, elevated right heart pressures and vascular resistance, while much weaker relationships were observed between plasma catecholamines and these haemodynamic abnormalities. These findings vary significantly from the findings of other workers in that the reverse situation has generally been observed. This is probably due to failure to delay recordings until the stress of catheterisation has abated. Hyperaldosteronism observed in patients with stable heart failure appeared to be largely due to diuretic-induced activation of the renin-angiotensin system. Activation of this system appears to maintain arterial pressure in the face of reduced cardiac preload and output induced by diuretic therapy. Vasoconstriction resulting from elevated plasma angiotensin II levels may contribute to increased afterload in heart failure, and this may ultimately be detrimental to the failing myocardium in the long-term, despite short-term symptomatic benefit provided by these agents.

The angiotensin converting enzyme inhibitor, enalapril, effectively reduced elevated angiotensin II levels. This was associated with a beneficial haemodynamic response which was most evident in those patients with greater initial activation of the renin-angiotensin-aldosterone system on the higher doses of frusemide. At a one to two month follow-up, exercise capacity had improved in these patients. Sustained benefit of this form of therapy was confirmed by a withdrawal study (Chapter 10): the cessation of long-term captopril therapy following a double-blind protocol demonstrated haemodynamic deterioration and reduced exercise capacity in those who were withdrawn from the medication.

Furthermore, significant symptomatic deterioration occurred in two patients while serious hypokalaemia developed in another.

A number of vasodilators have been assessed for efficacy in the ambulatory management of heart failure, but many lack sustained benefit. The development of tolerance to these agents may arise for several reasons. As the renin-angiotensin system has been implicated in the resistance to these agents as well as diuretic therapy, failure to block this system probably plays a major role in the reduction of effectiveness of many of these vasodilators. Once the patient fails to respond to sodium restriction or low dose diuretic therapy, angiotensin converting enzyme inhibitors will probably become the treatment of choice. Enalapril will probably supplant captopril because it produces fewer side-effects and hypotension is induced more gradually. Safety of this agent will pave the way for evaluation in less severely afflicted patients. Symptomatic, haemodynamic or exercise improvement is not likely to be great in mildly impaired patients, but the effect of angiotensin converting enzyme inhibition on prognosis and prevention of gradual decline in cardiac function will need to be investigated by studies involving large numbers of patients.

Turning to the role of the sympathetic nervous system in heart failure, other workers have demonstrated that depletion of myocardial norepinephrine occurs in severe heart failure, while receptor function remains normal. Stimulation of cardiac beta-adrenergic receptors supports the failing myocardium, while stimulation of alpha-adrenergic receptors produces vasoconstriction in some vascular beds, diverting blood to vital organs, but increasing ventricular afterload, which may ultimately be detrimental to cardiac function. Many positive inotropic agents, including several potent synthetic catecholamines, are currently being investigated in chronic heart failure, but their place in the ambulatory management of this syndrome remains in doubt. Administration of the beta-1 adrenergic agonist, prenalterol, produced a beneficial haemodynamic response consistent with its inotropic properties. Vasodilatation occurred either as a result of direct beta-receptor induced dilatation or withdrawal of increased activity of the sympathetic nervous system. Concomitant activation of the

renin-angiotensin-aldosterone system may diminish the overall effectiveness of this drug with long-term oral therapy, thus angiotensin converting enzyme inhibition may be necessary to achieve maximal benefit.

A group of Swedish authors have suggested that sympathetic overactivity may be deleterious in patients with dilated cardiomyopathy, contrary to current teaching. From empirical observations in non-controlled studies, they claim that beta-adrenergic blockade improves symptoms, cardiac size, exercise performance and prognosis in this condition. This casts doubt on our current concept of the role of the sympathetic nervous system in supporting the failing myocardium. From data presented in Chapter 8, I could find no difference in hormonal indices between patients with ischaemic heart disease and those with dilated cardiomyopathy. The study documented in Chapter 9 was the first placebo controlled, double-blind trial to investigate the effects of beta-blockade in patients with dilated cardiomyopathy. Heart size increased while exercise capacity declined on acebutolol. I could not support the Swedish findings and until their work is followed by a properly controlled study with an adequate number of subjects, beta-blockade in this condition cannot be recommended.

It is difficult to comment on the role of ADH in the patients in whom levels were measured. Generally, levels were within our laboratory range for healthy volunteers. ADH levels declined slightly during enalapril therapy, while prenalterol did not appear to effect levels in three patients. The data failed to show any close association with known or suspected stimuli of ADH release (arterial pressure, left ventricular filling pressure, plasma sodium or angiotensin II) although there was a significant correlation to frusemide dosage. Control of ADH secretion is multifactorial and complex, while the major routes of clearance from plasma have not yet been clarified in heart failure. Elucidation of the role of ADH in heart failure will require further study with better control of fluid intake and blockade of ADH action and/or secretion.

To conclude, the studies incorporated in this thesis contribute significantly to our understanding of the role of neurohumoral systems in the pathophysiology and management of heart failure.

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