STUDIES OF THE CARDIOVASCULAR EFFECTS OF INOTROPIC AGENTS AND VASODILATORS ON THE PULMONARY AND SYSTEMIC CIRCULATION IN MAN

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FORMAL DECLARATION

I declare that I have written the dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine; that it is based upon my own observations and that, except as indicated in the thesis, the data were collected, analysed and interpreted by me.

C G WATHEN
Many drugs have recently been introduced for the treatment of hypertension and heart failure. These drugs may primarily affect the heart or components of the peripheral circulation and may have adverse as well as beneficial effects. Although animal studies can give some indication of the mode of action, such drugs should be evaluated both by measurement of their effects on the circulation and by appropriate clinical trials to determine if there is any useful benefit. In this dissertation this principle has been applied to inotropic and vasodilator drugs used for treating heart failure and hypertension.

To study the circulatory effects of drugs, I have modified standard radionuclide methods and developed a technique to examine peripheral venous capacitance. The problems of assessing ventricular function when afterload changes have been studied. To assess benefit I have organised and conducted appropriate clinical trials.

The first section comprises two studies of drugs which modify inotropic state. The haemodynamic effects of the beta-adrenergic antagonist atenolol were examined in patients with previously untreated essential hypertension. Blood pressure was lowered but the underlying circulatory abnormalities including the elevated peripheral vascular resistance were not corrected. Patients with cor pulmonale were given the beta-adrenergic agonist pirbuterol and the cardiovascular effects compared with those of the pure vasodilator sodium nitroprusside. Pirbuterol was shown to act as a vasodilator with some selectivity for the pulmonary circulation but a minor positive inotropic effect was detected.

The second section reports studies where calcium channel antagonist vasodilators were evaluated in hypertension. The cardiovascular effects of nifedipine were studied at rest and during exercise in hypertensive patients with and without beta-adrenergic blockade. In contrast to atenolol, nifedipine reduced peripheral vascular resistance but a negative inotropic effect was observed. Therefore the newer calcium antagonist felodipine, which in animal experiments had been shown to be selective to the arterial circulation, was examined in patients and the lack of cardiac depression was confirmed. Following these promising results a clinical trial comparing felodipine with the most potent vasodilator available, minoxidil, in severe hypertension was undertaken. The results indicated that felodipine has an important role in the treatment of severe hypertension.

This work demonstrates how cardiovascular effects of inotropic agents and vasodilators can be assessed in intact man. Therapeutic benefit can only be assessed by adequate clinical trials.
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THE PURPOSE OF THIS THESIS

The mortality and morbidity of diseases affecting the cardiovascular system have been well documented. In the United Kingdom and Scotland in particular, premature death from ischaemic heart disease and chronic lung disease is higher than virtually anywhere else in the world. Developments in pharmacology have made it possible to modulate the circulatory abnormalities in right and left heart failure and hypertension and should allow improvements in management of patients suffering from these conditions. The treatment of right and left heart failure arising in a variety of pulmonary and cardiac diseases has changed little over the last twenty years and is aimed at ameliorating the consequences of low cardiac output. Digoxin is still used following the observation made in 1785 that the foxglove extracts were of benefit to patients with cardiac failure. The fluid overload seen in these patients as a consequence of the underlying defects of heart function is treated with diuretics. The prognosis in left heart failure associated with cardiac disease and right heart failure secondary to pulmonary disease remains poor. Development of new drugs, notably vasodilators, inotropic agents and drugs to counteract secondary endocrine effects have introduced new possibilities into the management of heart failure but the roles of the agents are not yet established. Because of the invasive nature of traditional methods used for studying cardiac function, such studies are limited and often the findings not applicable to chronic treatment.
In severe hypertensives, drug therapy has been shown to reduce the incidence of stroke and renal failure but for the vast majority of patients with a less severe form of disease, the greater amount of death and morbidity due to cardiovascular disease has not been reduced with the normalisation of blood pressure. Indeed, in mild hypertension where there is documented increase risk of cardiovascular disease, it has now been shown that the benefits theoretically obtained from the hypotensive effect of current drug therapy are not achieved. Adverse effects of drug therapy may increase the risk negating the benefits of such therapy. Because of the invasive nature of the standard techniques used to investigate the cardiovascular system, only a small number of patients and often those with the more severe form of disease have been studied and often the results obtained in patients with one type of disease have been applied to other groups of patients. Recently, it has been suggested that the increased resistance of the peripheral circulation which is a common feature of hypertensive patients is not corrected by the drugs most commonly used in the management of this condition and it is possible that other forms of therapy may be more appropriate.

Recent advances in nuclear medicine techniques make it possible to carry out non-invasive studies of cardiac function and the circulation in intact patients, and also allow repeat studies to be performed. In this Thesis, it is proposed to develop radionuclide techniques to study patients with right and left ventricular failure and hypertension and to assess circulatory abnormalities in the
heart, arterial circulation and peripheral veins. It is then proposed to examine the changes in the cardiovascular system produced by drugs which affect inotropic state, vasodilators and calcium antagonists in relation to the abnormalities detected in these groups of patients. The pathophysiological data produced might have clinical value in suggesting the most appropriate forms of treatment for patients with the conditions studied. It is then proposed to carry out appropriate clinical trials of inotropic therapy in heart failure and vasodilator therapy in hypertension to establish if there is any benefit over and above that of the current standard therapies.
CHAPTER 1
Nervous and hormonal control of the heart and the blood vessels which make up the systemic circulation maintain adequate tissue perfusion in the many physical states encountered. Under normal circumstances cardiac output, blood pressure and peripheral vascular resistance are modulated short-term to supply the metabolic demands of the body and in the longer term the circulating blood volume is closely regulated to the optimum. In disease states affecting the cardiovascular system, there is an imbalance in these regulatory and control mechanisms and often compensatory factors come into play. Below I shall consider the effects of drug therapy on the circulation in left and right heart failure and hypertension and assess how the beneficial effects might be assessed to obtain optimum benefit in these disease states.

A brief account of cardiovascular abnormalities seen in heart failure and hypertension is required for an understanding of the actions of the drugs currently used in the management of these diseases and to assess how clinical benefit might best be achieved.
DRUG THERAPY OF HEART FAILURE

Historical review

In 1749 Senac published his textbook on heart disease and this contained the first clear account of pharmacological treatment of any cardiac disease. He described the value of venesection and sedation in the management of heart failure and also the use of quinine for treating "rebellious palpitations" or arrhythmias. Several years later in 1775 William Withering started to study the effects of foxglove extracts in patients with dropsy (cardiac failure) after noting benefit in a patient he was treating with the extract because of its emetic properties. Ten years later he published his renowned monograph on foxglove extracts (Withering, 1785) noting that foxglove had been introduced as an emetic by Fuchs in 1542. Attempts were made to purify the extracts and in 1847 Nativelle working in Paris isolated digitoxin. Two hundred years after Withering's observations digoxin therapy is widely used for the treatment of heart failure and the indications and dosage are little different from his original recommendations.

Senac's observations of the beneficial effects of sedation with opiates and venesection in patients with heart failure (1749) are both still valid today and after much research into the beneficial effects of opiates in patients with acute pulmonary oedema, it appears that the sedative effect is probably the most important (Vismora et al, 1976). Venesection became very popular with many eminent cardiologists despite the realisation that it produced
anaemia. The improvement in the symptoms of pulmonary oedema was widely thought to relate to a reduction in blood pressure (afterload) rather than the reduction of filling pressure (preload) which is now realised to be the beneficial effect (East, 1958).

Nitrate therapy for 'angina pectoris' was introduced by Lauder-Brunton in Edinburgh in 1867 when he gave patients with chest pain and breathlessness amyl nitrite in an attempt to lower blood pressure. He had observed two types of 'angina pectoris', the first which fits the classical description of angina with chest pain and the second which had typical features of pulmonary oedema. He was aware of the beneficial effects of venesection for this second group of patients with dyspnoea and reasoned that blood loss, and therefore amyl nitrite, was effective through reducing blood pressure. Murrel (1879) confirmed the benefits of nitroglycerin several years later. In retrospect the beneficial effect of the nitrates in patients with breathlessness were probably due to the beneficial effect of venous pooling in those patients with pulmonary oedema.

There were no further significant developments in medical therapy of heart failure until the introduction of mercurial compounds as diuretics but the benefits of fluid restriction were known since the 800 cc skimmed milk diet of Karell introduced in 1866 (see White 1957). In 1903 Widal and Lemierre were able to show that it was the sodium restriction of this and other diets which were beneficial. In 1877 Southey, using another approach, developed needles which could be positioned in dependent soft tissues to exploit the
beneficial effects of fluid loss in heart failure (see White 1957).

When the mercurial antisyphilitic agent merbaphen was introduced in 1920, Vogl, a medical student and clinical clerk working with Saxl in Vienna soon observed its diuretic properties and was able to demonstrate benefit in patients with heart failure (Vogl, 1950). Mercurous chloride had been used as a diuretic in the sixteenth century by Paracelsus and was contained in the "Guy's Hospital Pill" (mercurous chloride, squill and digitalis) used for treating heart failure in the 19th century. From merbaphen more potent and less toxic mercurial diuretics were developed and widely used before being displaced by more modern carbonic anhydrase inhibitors and thiazide diuretics.

Until very recently combinations of digoxin, diuretics and opiates with the occasional use of nitrates have been the drugs used to treat acute and chronic heart failure (Braunwald, 1981). The failure of these drugs to completely ameliorate symptoms or cure patients has led to the recent search for other approaches to the management of heart failure. Such developments depend on an understanding of the cardiovascular abnormalities of heart failure and from this production of pharmacological adjustments which might prove beneficial.

LEFT VENTRICULAR FAILURE

Left ventricular failure has been defined as a situation where
cardiac output is inadequate to meet the metabolic needs of the individual (Lewis, 1933). This can arise either due to reduced myocardial contractility or, less commonly, increased demands on the heart such as those produced by rheumatic valvular disease, arterio-venous fistulae or states of increased metabolic activities, notably hyperthyroidism (Braunwald 1984). The reduced myocardial contractility caused by ischaemic heart disease and cardiomyopathy is referred to as myocardial failure to distinguish it from heart failure and secondary circulatory failure when the primary deficit is not necessarily in the pumping action of the heart (Braunwald, 1981). In the presence of myocardial failure, three compensatory mechanisms are activated to maintain the circulation. The first is the increased contraction of the functioning myofibrils in the presence of increased stretch produced by the increased distension of the left ventricle (or increased left ventricular end diastolic blood volume), by the principle named after Frank and Starling (Frank 1959; Chapman and Mitchell, 1965). The second mechanism brought into play is increased secretion of catecholamines from the sympathetic nervous system and adrenal medulla which have a positive inotropic effect on the heart. Finally there may be hypertrophy of the functioning myofibrils to augment the mass of contractile tissue. To a certain extent therefore myocardial failure may be present without overt heart failure. There are clearly limitations to the degree of compensation possible and beyond that point, heart failure develops.

Clinical evidence of heart failure will initially become apparent
during exercise when the demands on the heart are greatest. Failure of the heart to maintain stroke volume despite increasing end diastolic volume results in low cardiac output, under-perfusion of the tissues and in particular the kidneys. Ultimately fluid retention develops as a result of reduced renal perfusion and the circulating blood volume expands increasing the preload or diastolic filling of the heart. Initially this improves myocardial function by the Frank-Starling mechanism but the increased preload, or venous pressure, also produces pulmonary and peripheral oedema.

The fluid accumulation is aggravated by activation of the renin angiotensin aldosterone mechanism as a result of the increased renin secretion which results from reduced renal perfusion (Cody and Laragh, 1983). The sympathetic nervous system is activated as a reduction in cardiac output tends to lower peripheral blood pressure. The noradrenaline released is powerfully inotropic but also produces vasoconstriction and thereby increasing the afterload and demands on the heart. The angiotensin 2 generated by the increased renin secretion in conjunction with the activation of the sympathetic nervous system tends to maintain arterial pressure by vasoconstriction of blood vessels supplying the kidneys, skin and splanchnic circulations whilst preferentially maintaining blood flow to the heart and brain. There is also constriction of the venous bed by the sympathetic nervous system leading to a shift of blood from the peripheral venous system to the heart which tends to increase the already elevated preload beyond the point at which myocardial function will increase such that there is continuing
deterioration of cardiac function (Cohn et al, 1981).

The role of the natriuretic peptides released from the atria as a result of the increased stretch are not yet understood (Genest, 1986) but presumably there is an inadequate compensation for the fluid overload. One further compensatory mechanism for the decreased cardiac output deserves mention and this is a shift of the oxygen haemoglobin dissociation curve towards a decreased affinity of haemoglobin for oxygen produced by an increased level of red cell 2-3 diphospho-glyceroate when there is tissue acidosis. This helps to improve the oxygen supply to the tissues (Woodson et al, 1970) despite underperfusion.

RIGHT VENTRICULAR FAILURE IN COR PULMONALE

Studies of right heart failure as a consequence of pulmonary disease have been more limited, most are acute or short term and relate to patients with Cor pulmonale as a result of chronic bronchitis and emphysema or patients with primary pulmonary hypertension (Oakley, 1985). The common abnormality in these conditions is an elevation of pulmonary artery pressure and pulmonary vascular resistance (Fishman, 1976). This leads to cor pulmonale which the WHO have defined as right ventricular hypertrophy resulting from disorders that affect either the structure or function of the lungs (World Health Organisation, 1963). In cor pulmonale occurring as a result of chronic bronchitis there is no clear evidence of primary failure of the right ventricular myocardium and only when the pulmonary
vascular resistance is extremely high in patients with primary pulmonary hypertension does this does occur (Fishman, 1976; Richens and Howard, 1982; Rozkovec et al, 1985). In Cor pulmonale there is evidence that prognosis is related to the degree of pulmonary hypertension (Weitzenblum et al, 1981) but it is interesting that evidence of 'right ventricular failure' as evidenced by elevation of the jugular venous pressure and peripheral oedema occurs at much lower levels of pulmonary artery pressure in patients with chronic bronchitis than those present in primary pulmonary hypertension without any evidence of right heart failure (Fishman and Pietra, 1980). The oedema in patients with chronic bronchitis and cor pulmonale tends to develop during acute exacerbations (which are often precipitated by chest infections) and it has been suggested that pulmonary vascular resistance increases further in such acute cor pulmonale (Herles et al, 1968). Although hypoxia is a potent pulmonary vasoconstrictor (Abraham et al, 1970) and long-term controlled oxygen therapy has been shown to lower pulmonary vascular resistance (Weitzenblum et al, 1985) and improve prognosis in patients with severe chronic bronchitis (Medical Research Council, 1981; Nocturnal Oxygen Therapy Trial Group, 1980), it has been suggested that the hypercapnia which is peculiar to chronic bronchitis and emphysema and not the hypoxia (which is common to many respiratory diseases) is the cause of the oedema (Campbell and Short, 1960). It has been argued by Richens and Howard (1982) that hypercapnia may be the cause of reduced renal blood flow which has been observed in patients with cor pulmonale (Aber and Bishop, 1965). This fall in renal blood flow would produce activation of the renin
angiotensin aldosterone axis and could lead to salt and water retention. Measurements of the renin and aldosterone in Cor pulmonale are sparse but Tomaszewski et al (1975) noticed elevated plasma renin activity in 8 out of 11 patients with Cor pulmonale and peripheral oedema. These findings may explain why there is relatively little benefit from digoxin in the treatment of cor pulmonale because they suggest that fluid overload and not primary right ventricular muscle failure is the cause of the condition. Diuretics remain the mainstay of treatment. Unfortunately this treatment remains unsatisfactory and the prognosis is poor (Weitzenblum et al, 1981).

MODERN DRUG TREATMENT OF HEART FAILURE

Digoxin
The inotropic action of digoxin is still not fully understood but many investigators have concluded that digoxin increases the availability of calcium ions to the contractile proteins (Lee and Klaus, 1971). It is also known that digoxin binds to and inhibits the membrane of sodium-potassium adenosine triphosphatase (Na⁺ K⁺ ATPase) on cell membranes leading to an increase in the intracellular concentration of sodium ions. This in turn has been shown to increase the sodium-calcium exchange within the cell increasing calcium influx and therefore raising the intracellular calcium ion concentration. This is thought to be the stimulus to actinomyosin contraction. In addition to its inotropic action, digoxin and the other cardiac glycosides have electrophysiological effects which do
not need to be considered here.

The clinical role of cardiac glycosides in heart failure remains controversial (Johnstone and McDevitt, 1979; Seltzer, 1981) but recent studies have shown that the inotropic action is maintained with chronic usage (Petch, 1979; Arnold et al, 1980; Murray et al, 1982). Because of the significant toxicity of this group of drugs (Poole-Wilson, 1984), the narrow therapeutic margin and the response limited in most patients in sinus rhythm, the clinical effect is usually modest (Johnston, 1985). However, because it is absorbed after oral administration it has for many years been the only inotrope available for use in chronic heart failure (Smith and Haber, 1973). Alternative orally active inotropic agents are being developed (Editorial, 1983; Glover et al, 1985).

Diuretics
Diuretic drugs will increase the urinary excretion of sodium and water. This can be achieved by a direct action on the kidney, by sodium and water absorption from the tubule or indirectly by increasing renal blood flow. This latter group includes drugs such as digoxin and dopamine and will not be considered further. Diuretic compounds with a direct action on tubule can be broadly classified into three groups, those affecting the proximal tubule such as carbonic anhydrase inhibitors, for example, acetazolamide, those affecting the Loop of Henle, the so-called loop diuretics such as frusemide and ethacrynic acid and diuretics which affect the distal nephron, the thiazides and potassium conserving diuretics.
The diuretics are used to increase renal salt (sodium) and water excretion, lower the filling pressures of the left and right atria and therefore relieve the symptoms of pulmonary and peripheral oedema. They do not directly increase cardiac output and may, in fact, under certain circumstances reduce it through a salt and water induced plasma volume contraction (Braunwald, 1984). Complex feedback mechanisms will increase the tubular sodium absorption when diuretics are given thereby tending to counter the diuretic effect. In chronic dosage there is increase in tubular reabsorption of sodium at the sites where the diuretic is inactive until salt balance is re-established at a new level and homeostasis is re-achieved with a lower total body sodium (Swales, 1975). This increase in sodium reabsorption can to some extent be overcome by using combinations of diuretics acting on different parts of the nephron (Wollam et al, 1982). Furthermore by reducing blood volume diuretics activate the renin-angiotensin system increasing secretion of aldosterone (and probably suppressing atrial natriuretic peptide secretion) which will also tend to increase tubular sodium reabsorption.

Reduction of circulating blood volume beyond a certain point by diuretic therapy will lead to a lowering of left ventricular end-diastolic pressure to a degree whereby cardiac output is reduced through the Frank-Starling mechanism from inadequate preload. At this point renal blood flow and glomerular filtration rate will decline reducing further the effectiveness of the diuretic with the onset of renal failure.
Although the loop diuretics have been observed to cause an increase in renal blood flow when used acutely, this does not appear to occur with chronic dosage. The mechanism of this increase is not clear (Stein et al, 1978). Independent of their diuretic effects, loop diuretics have been noted to increase peripheral vascular compliance and reduce venous return (Dikshit et al, 1973). This is of benefit in acute cardiac failure in the presence of pulmonary oedema because of the beneficial effects on cardiac filling pressures but in the long term could lead to reduced renal blood flow in the face of maintained intravascular volume if the venous pooling persists.

Diuretics have remained the mainstay of treatment of cardiac failure because of their effect on sodium and water excretion since the introduction of the organic mercurial compounds but because of the compensatory regulating mechanisms discussed above, their effect is limited. Their use is associated with considerable adverse effects, notably hypokalaemia, metabolic alkalosis, hyponatraemia, hyperuricaemia, carbohydrate intolerance, and ototoxicity due to the effects on fluid and electrolyte balance. These limitations have stimulated the search for newer pharmacological agents.

**Vasodilators**

In recent years there has been a trend to introduce vasodilators into the management of chronic left ventricular failure. The actions of these drugs broadly divide into two classes. The first group are those which reduce the venous filling pressure or preload such as
nitrates (Franciosa et al, 1978) and the second group reduce arterial pressure by arterial vasodilation, so called afterload reducing agents. The latter group are in general similar to antihypertensive drugs notably hydralazine (Franciosa et al, 1977). The role of these two classes of drugs is not yet fully established and although they have been shown to be beneficial when given acutely, there is little data on their value in chronic usage. Some studies suggest that tachyphylaxis occurs after a period of 4-6 weeks of vasodilator therapy such that prolonged therapy is of little value (Packer et al, 1979). A large study recently reported from the United States suggests that the combination of arteriolar and venodilator drugs, nitrates and hydralazine may be of benefit to certain patients with moderate "congestive" or left heart failure and might improve prognosis (Cohn et al, 1986). This study underlined the extremely poor prognosis for patients with left ventricular failure (Kannel, 1972; Glover and Littler, 1987) and the difficulty in determining whether any particular treatment is beneficial. Further, the selection criteria for patients used by the Veterans Administration for this study means that the results might not be more widely applicable.

The recent introduction of the angiotensin converting enzyme (ACE) inhibitors which have the combined beneficial effects of arterial vasodilation and counteracting the sodium retaining effects of aldosterone (which is often marked in cardiac failure for the reasons outlined above) has provided some interest (Turini and Brunner, 1982) but their place in the management of heart failure is not yet
Assessment of vasodilators has been difficult for two reasons. Firstly, in intact man it is difficult to separate changes in myocardial function which occur primarily due to increased myocardial contractility and those which occur second early from reduction in the aortic pressure or load against which the ventricle is pumping. There is disagreement as to which assessments best help determine the action of drugs on the heart and circulation in man but there is considerable evidence that studies allowing simultaneous assessment of pressure and volume for the left ventricle and hence the construction of a Frank-Starling type relationship at end-systole allow differentiation between inotropic effects and vasodilation (Sagawa et al, 1977; Miller et al, 1981). Unfortunately these measurements have required invasive studies and have therefore been limited to patients who in general have extremes of heart failure requiring catheterisation of the left and right sides of the heart. Further, the assessments cannot be carried out repeatedly and therefore long-term effects after compensatory changes have taken place are not clear. The use of radionuclide investigation of ventricular volume might potentially allow a non-invasive assessment of changes in end-systolic pressure and volume. The second problem is that assessment of change in cardiac function have not been shown to correlate with either patients' symptoms or exercise tolerance which are probably better assessments of any benefit from therapeutic intervention (Benge et al, 1980; Franciosa et al, 1981). Further assessment of vasodilator therapy is required.
DRUG TREATMENT OF COR PULMONALE

Diuretics
In acute cor pulmonale, diuretics will reduce oedema and alleviate the symptoms of fluid retention (Campbell et al, 1975). From the discussion above, they would appear to be a rational therapy in this situation. Diuretics are generally prescribed for chronic therapy in patients with cor pulmonale but there appear to be no studies to confirm the clinical impression that they are beneficial in the long term (Heineman, 1978). Oedema occurs in acute cor pulmonale in patients already taking substantial diuretic therapy (Campbell et al, 1975) and it seems unlikely that diuretics will have any beneficial effects on the underlying pulmonary abnormalities.

Vasodilators
Recently attention has been turned to studying the use of vasodilator therapy, usually in an attempt to produce pulmonary vasodilation and reduce the elevated pulmonary artery pressure. Again there are significant technical difficulties in distinguishing true changes in pulmonary vasomotor tone and changes which are secondary to changing cardiac output. As yet there is no substantive evidence that any vasodilator has beneficial therapeutic effects (Howard, 1983) and some have been shown to increase ventilation perfusion mismatching in the lungs, further aggravating the hypoxaemia (Melot et al, 1984) although this does not appear to be true of hydralazine (Keller et al, 1984). Indeed the calcium antagonists used as pulmonary
vasodilators might increase mortality (Packer et al, 1984). The fundamental objective of lowering pulmonary artery pressure to improve exercise tolerance and survival may be falacious. The drug almitrine bismesylate which is a peripheral chemoreceptor stimulant used to increase ventilation (Stradling et al, 1982) has been shown to raise pulmonary artery pressure in patients with chronic bronchitis acutely (MacNee et al, 1984) and chronically (Howard et al, 1987) but despite this in a placebo controlled double-blind trial of almitrine in such patients there was probably an improvement in their condition and no increased mortality (Voisin, 1985): clearly other parameters are important. Further investigation of the right ventricular function; ventilation perfusion matching and consequent combined cardiac/pulmonary function, with the effects of modifying these parameters are required.

Inotropic agents
The aim of inotropic therapy is to improve the right ventricular response to increased demand from pulmonary hypertension but as outlined above this may not be a rational approach. Digoxin appears to be of no benefit in the absence of arrhythmias (Green and Smith, 1977; Brown et al, 1984) and no other drug investigated is free of pulmonary vascular or broncho-dilating properties such that the effect on inotropic state have not been assessed (Howard, 1983).

In this thesis early studies on the assessment of right ventricular function by radionuclide angiography in patients with chronic bronchitis to enable this are described along with an acute study to
assess the effects of the combined inotropic and vasodilator B-adrenoceptor agonist pirbuterol on the pulmonary circulation.
Historical review
Although Hales had directly measured arterial blood pressure in a horse in 1733 it was only in 1828 that Poiseuille described a method applicable to man. Subsequent developments in indirect sphygmonanometry by Von Basch, Riva-Rocci and Korotkow between 1881 and 1905, made it possible to measure blood pressure in patients and it became apparent that high blood pressure was associated with disease (see Pickering, 1964).

Although Baker had noticed the beneficial effect of veratrum alkaloids in treating eclampsia in 1859, and this had subsequently been confirmed by Barnes (1873), neither realised that the beneficial effect was a reduction in blood pressure. Lauder Brunton (1867) used amyl nitrite to treat angina because he was aware that it was hypotensive but the first attempts to reduce blood pressure in hypertensive patients were not pharmacological and were carried out many years later. In 1920 Allen introduced a low salt diet for hypertension and was able to show benefit in patients with severe or accelerated phase hypertension (Allen and Sherrill, 1922). Several years later Rowntree and Adson (1925) described the operation of surgical sympathectomy believing that hypertension was caused by an over-active sympathetic nervous system. Widespread use of dietary salt restriction followed Kempner's demonstration of the benefits of the rice-fruit (low sodium) diet known by his name (1948). These very low salt diets were not palatable and the search for agents to
increase salt excretion led to the development of diuretics. Freis and his colleagues (1957) demonstrated the natriuretic and hypotensive effect of chlorthiazide, commenting on the lack of benefit seen with the earlier mercurial diuretics and carbonic anhydrase inhibitors in hypertensive patients. Thiazide diuretics remain one of the most widely used groups of antihypertensive agents.

Although surgical sympathectomy was not a very reliable way of treating hypertension (Pickering et al, 1961) the observation that inhibition of the sympathetic nervous system lowered blood pressure led to the search for agents to inhibit the effects of catecholamines. The ganglion blocking agent hexamethonium was introduced by Henry Dale in 1915 (Burns and Dale, 1915) but its lack of specificity led to serious hypotensive side effects related to the widespread autonomic blockade produced. Further developments led to the introduction of phenoxybenzamine (1947), bretylium (1959) and guanethidine (1960), which were selective for adrenergic nerves, were better tolerated but which were still associated with profound postural hypotension and other unwanted effects (Dollery, 1973).

Black and his group working from the data and classification of adrenoceptors by Alquist (1948) developed the first beta-adrenergic blocking drug, propranolol in 1960 (Black and Stephenson, 1962). This drug and its successors are associated with far fewer adverse effects such that beta-adrenergic blocking agents (beta-blockers) have gained wide acceptance in the treatment of hypertension.
Although earlier studies had shown an improvement in prognosis from treating patients with accelerated phase hypertension, it was only in 1967 that the Veterans Administration convincingly demonstrated the merits of treating moderate to severe hypertension (Veterans Administration Cooperative Study Group, 1967). This increased the numbers of patients who were thought to require treatment for hypertension enormously and most of these patients requiring treatment were asymptomatic such that the need for drugs with a minimum of adverse effects became more acute. The Veterans Administration were able to show a reduction in the incidence of stroke and renal failure from treating hypertension and this has been confirmed in numerous subsequent trials but as yet the increased risk of cardiovascular disease (for the purposes of this thesis that is ischaemic heart disease) in hypertensive subjects has been little altered by treatment of their hypertension (Oliver, 1982; Medical Research Council Working Party, 1985).

ESSENTIAL HYPERTENSION

The aetiology of essential hypertension is unknown, and indeed there may be several mechanisms leading to the observed elevation of blood pressure and peripheral or systemic vascular resistance which characterise this condition (Lund Johansen, 1980). The interaction of the cardiovascular system, the kidney and the neuro-endocrine control mechanisms which regulate the circulation have all been shown to be deranged in established hypertension. Below I shall consider those aspects of the cardiovascular system which seem to be central
to the development of hypertension, and amenable to therapeutic intervention.

**CARDiac Abnormalities in Essential Hypertension**

Several groups have demonstrated that in young patients with "borderline" or "mild" elevation of blood pressure resting cardiac output is elevated by about 15%, largely due to an increase in heart rate but also due to a rise in stroke volume (see Lund Johansen, 1983). However, Birkenhager and de Leeuw (1984) have argued that this finding is an emotional artefact. They observed that a "seasoned" or familiarised group of patients have lower cardiac outputs than a "naive" or new group of patients and claim that when this is taken into account, as in their studies, the haemodynamic differences between the hypertensives and normal subjects no longer exists. At present there is still debate as to whether there is a real increase in cardiac output in borderline hypertensive subjects and this might best be studied using non-invasive techniques.

Peripheral or systemic vascular resistance is within the normal range in such subjects with borderline hypertension and rises with time; this increase is particularly apparent on exercise. There appears to be a slight fall in resting cardiac output when arterial blood pressure has become elevated, and very early in this progression alterations in the left ventricle producing a reduced compliance can be detected (Fouad et al, 1980). This is associated with increased left ventricular mass and wall thickness (Cohen et al, 1981; Schieken
et al, 1981), and probably explains the lower stroke volume initially observed during exercise in hypertensive subjects (Lund Johansen, 1983).

Hence there are undoubtedly structural and functional changes in the circulation at a very early stage in hypertension. It is not known at what stage these changes develop or why they do but it appears that the vascular abnormalities which increase the peripheral resistance (Folkow et al, 1973) or afterload probably lead to the changes noted within the heart (Birkenhager and de Leeuw, 1984). There is increasing evidence that the increase in vascular tone results from neuro-endocrine mechanisms activated by the alterations within the circulating blood volume (Guyton, 1981).

**BLOOD VOLUME AND DISTRIBUTION IN HYPERTENSION**

It has been noticed in many parts of the world that sodium intake is related to the incidence of hypertension (Gleiberman, 1973) and there is compelling data showing that a high salt intake will elevate blood pressure in some individuals as discussed by de Wardener and McGregor (1982), and Lee (1981). It has been proposed by these authors that the high salt intake unMASKS an inability of the kidney in individuals susceptible to hypertension to excrete a sodium load and Lee (1981) has suggested that there may be a failure to synthesise the natriuretic compound dopamine in the kidney. This inability to excrete excess sodium is probably genetically determined Such an inherited abnormality of sodium excretion has elegantly been
demonstrated by Dahl (1977) in the Brooklin rat. Thus sodium retention would occur and lead to increased blood volume. There are several hypotheses as to how this would lead to the development of sustained hypertension. Guyton (1981) has explained how this might lead to the development of hypertension which in turn he argues would return the blood volume towards normal. He proposes that with chronic blood volume expansion, reflexes are damaged such that the compensatory fall in vascular resistance to maintain blood pressure at the normal level does not occur.

However, blood volume in hypertensive subjects is known to be low (Tarazi et al, 1968) and it has been proposed that the sodium retention leads to release of natriuretic factors (de Wardener and McGregor, 1982). There is now clear evidence that atrial natriuretic peptide (ANP) is produced by the right and possibly left atria in response to atrial stretch and in addition to increasing salt excretion by the kidney this substance decreases venous tone (Genest, 1986). One group has very recently found ANP to be elevated in the plasma of patients with established essential hypertension (Sagnella et al, 1986) although others have not found this elevation (Genest, 1986) and as yet there is no clear idea of the significant of ANP in relation to the development of hypertension.

Other natriuretic factors have been identified in hypertensive subjects and these are ouabain like sodium-potassium adenosine triphosphatase pump (Na\(^+\)K\(^+\) ATPase) inhibitors (Poston et al, 1981; de
Abnormalities of sodium transport have been demonstrated in the membranes of red blood cells and more consistently in white blood cells from hypertensive patients have also been described. Such abnormalities have been attributed to changes in cell membrane lipids (Bing et al., 1986). This would have the same effects as the putative plasma Na\(^{+}K^{+}\) ATPase inhibitor of raising intracellular sodium concentration which Blaustein (1977) has suggested would increase the tone of vascular smooth muscle cells by reducing the intracellular plasma calcium concentration through the sodium-calcium exchange mechanisms.

An increase in smooth muscle vascular tone in veins produced by either mechanism would explain the increased venous tone noted in hypertension (Safar and London, 1985) and the shift of blood from the peripheral to the central compartment as evidenced by the increased central venous pressure (Safar et al., 1974) and intrathoracic blood volume (Ulrych et al., 1969; London et al., 1978; McKay et al., 1984) observed in patients with essential hypertension. This increased central blood volume could be associated with the release of ANP by the increased distention of the right atrium or, as Genest has argued (1986) insufficient release of ANP due to reduced sensitivity of the right atrium from chronic stretching such that there is inadequate vasodilator ANP. Clearly further study, probably using more sensitive assays for ANP in conjunction with cardiovascular studies, are required. Further analysis of the effects of this shift of blood to the central compartment is not possible but de Wardener and McGregor feel that this would lead to secretion of the proposed Na\(^{+}K^{+}\)
ATPase inhibitor, possibly from the hypothalamus by a neural mechanism (de Wardener and McGregor, 1982). The effect of increasing or decreasing the central blood volume in hypertensive subjects have been little studied but Krauss and his colleagues (1972) have demonstrated that beta-blockade with propranolol prevented the increase in central blood volume produced acutely by saline infusion in hypertensive subjects by reducing the venous return to the heart. It is not at all clear how propranolol might have this effect because beta-blockade would be expected to reduce peripheral vascular compliance and have the opposite effect.

MODERN DRUG TREATMENT OF HYPERTENSION

The reduction of blood pressure in hypertensive patients including those with fairly mild hypertension has been shown to be beneficial (Editorial, 1984; Breckenridge, 1985) but there is no evidence that the type of therapy used affects prognosis. The current drug treatment of essential hypertension is largely empirical and prescribing trends aim towards reducing drug-related adverse effects (Editorial, 1986). Much research therefore has been devoted to developing drugs which are better tolerated. In the main thiazide diuretics and beta-blockers are the most widely used treatment but in neither case is it clear why these drugs are effective. Vasodilators have also been used, usually when an inadequate response has been obtained with beta-blockers and diuretics or when these drugs are contraindicated. Centrally acting drugs such as clonidine and methyl-dopa have adverse effects and are being
superseded by other agents.

Diuretics

Diuretics undoubtedly produce a loss of sodium and water in the first few weeks of therapy but in hypertensive subjects on treatment for more than 6 or 8 weeks, it has been noted that the plasma volume and sodium content return to the pre-treatment values at a lower level of blood pressure (Swales, 1975). It has been suggested that diuretics and the thiazide-like compound diazoxide leach sodium or possibly calcium from the arterial vessel walls producing vasodilation (Hollander et al, 1958). This does not appear to be the hypotensive effect because diuretic therapy produces a fall in cardiac output in hypertensive patients, and not the expected increase from vasodilation (Shah et al, 1978). Tobin (1974) has suggested that this reduction in cardiac output produces a resetting of the regulatory mechanisms controlling the circulation such that the blood pressure is reduced. Diuretics were thought to be relatively safe but recent studies, notably the MRC Mild Hypertension Trial (1986) have shown that the incidence of side-effects from thiazide diuretics is very considerable, notably impotence and gout along with the well recognised problems of hyperglycaemia, hyperlipidaemia and hypokalaemia. Similar findings have been made in a trial of more elderly people with hypertension (Amery et al, 1985). One large trial of primary prevention of coronary heart disease (Multiple Risk Factor Intervention Trial Research Group, 1982) concluded that diuretic therapy for hypertension might increase cardiovascular risk although the validity of this finding has been questioned
These results have been obtained with doses of diuretic which may be higher than required to control mild hypertension and if this is the case a lower incidence of side effects would be expected with a reduction in diuretic dose.

**Beta-adrenergic blocking agents**

The mechanism of antihypertensive action of beta-blockers is not understood. There is good evidence that renin release from the juxta-glomerular cells of the kidney is mediated by beta-adrenergic nerves (Johns and Singer, 1974) and it has been suggested that a reduction in renin release and hence activity of the renin angiotensin system was responsible (Laragh, 1973), but this finding has been inconsistent (Hamer, 1976). However, beta-blockers effectively lower blood pressure in patients with low plasma renin activity and it has been extremely difficult to show that changes in the renin angiotensin system correlate with the hypotensive effect (Leonetti et al, 1975). Further beta-blockers which do not suppress renin activity (for example oxprenolol and pindolol) and cardioselective beta-blockers are effective antihypertensive agents (Hamer, 1976). Another view has been that the reduction in cardiac output which can be detected in patients given beta-blockers might be responsible (Lund-Johansen, 1980). However, beta-blockers such as pindolol and oxprenolol which do not produce a reduction in cardiac output are equally effective antihypertensive agents and in the long term treatment of hypertension with a variety of beta-blockers there does not seem to be any relation between the changes in blood
pressure and reduction in cardiac output (Man in't Veld and Schalekamp, 1983). A central action of these drugs seems unlikely as water soluble compounds which do not cross the blood brain barrier, for example atenolol, are no less effective. In view of the widespread use and effectiveness of beta-blockers in the management of high blood pressure, it would be very beneficial to know how they exerted their antihypertensive effect. In this way it might be possible to devise more selective drugs which would not have the unwarranted side-effects noticed with chronic beta-blockade (Medical Research Council, 1986).

Vasodilators

An increasingly attractive option for the management of hypertension is the use of vasodilators (Koch-Weser, 1974). This rather heterogeneous group of compounds includes the direct arterial vasodilators such as hydralazine and the much more potent compound minoxidil, alpha-blockers such as prazosin, the calcium antagonist compounds, and more recently the angiotensin converting enzyme (ACE) inhibitors. The direct arterial vasodilators including hydralazine and minoxidil have been noted to produce tachyphylaxis with rebound tachycardia and also significant fluid retention in addition to well recognised problems not associated with their antihypertensive effect (McAreavy et al, 1984). Generally they have all been used in combination with beta-blockers and diuretics but the more recently available calcium antagonist and ACE inhibitor drugs do not seem to have been associated with this tachyphylaxis and in general have been effective when used as a single agent (Lederballe Pederson and
Michelsen, 1978; Edwards and Padfield, 1985). However, the effectiveness of ACE inhibitors is significantly increased when combined with diuretic and beta-blockers have been found to be usefully employed in combination with calcium antagonists to reduce the incidence of the adverse effects from vasodilation. Therefore assessment of these compounds in an appropriate population particularly in the combinations commonly used in clinical practice is important. So far such research has been limited and further work is indicated to establish more precisely the role of these drugs in relation to the cardiovascular system.

Until the aetiology of hypertension is understood it will be impossible to devise specific antihypertensive compounds but study of abnormalities present in essential hypertension and the effects of pharmacological intervention should enable the more rational use of the drugs available to modulate the circulation for the benefit of the patients.
CONCLUSIONS

From the above discussion it can be seen that evaluation of the benefits of drugs in clinical practice can be difficult and has often in the past only been established by chance observations and uncontrolled assessment. Benefits of drug therapy can be shown by comparison with a placebo but such trials require large numbers of patients and a considerable amount of time. As more drugs become available, it becomes more important to compare the benefits of several of the most promising compounds; indeed a combination of drugs may be the most beneficial therapeutic regimen. The clinical use of hydralazine described above provides a good example. This drug was synthesised in 1950 and has been in clinical use since 1960 but only in 1986 did the Veterans administration show that this drug, when used with nitrates in addition to standard diuretic and digitalis therapy prolonged survival in a selected group of patients with heart failure (Cohn et al, 1986). The authors suggest that this combination may already be bettered by the ACE inhibitors. A more rational approach to drug assessment is required.

Development of the clinical use of drugs can be considered in two phases:

1. Determination of the acute effects of the drug on the system under investigation, in the case of the circulation preload, afterload and contractility of the myocardium.
2. Longer term studies of symptomatic benefit, morbidity and survival.

From the knowledge of heart failure and hypertension available it is possible to suggest which modulation of the circulation is likely to be beneficial, to test this with appropriate drugs and if promising results are obtained go on to a clinical trial in the group of patients most likely to benefit from the therapy. The recent introduction of non-invasive radio-isotope studies of the circulation offers an easier way to assess the effects of drugs on the heart and peripheral circulation. In this thesis using this approach it is proposed to study the important effects of drugs which affect cardiac contractility and vasodilators in patients with cardiovascular disease and then carry out appropriate trials to assess clinical benefit.
CHAPTER 2
CARDIAC CATHETERISATION AND CONTRAST ANGIOGRAPHY HAVE BEEN THE METHODS USED TO ASSESS LEFT VENTRICULAR PERFORMANCE (Hamer, 1978). UNFORTUNATELY THESE INVASIVE TECHNIQUES ARE NOT WITHOUT SIGNIFICANT MORBIDITY AND SOME MORTALITY. FOR THESE REASONS SERIAL MEASUREMENTS AND REPEATED STUDIES ARE NOT PRACTICABLE. THIS HAS STIMULATED THE DEVELOPMENT OF METHODS FOR ASSESSING CARDIAC FUNCTION NON-INVASIVELY. M-MODE AND TWO DIMENSIONAL ECHOCARDIOGRAPHY HAVE PROVED TO BE SOMEWHAT INACCURATE AND VERY DEPENDENT UPON THE SKILLS OF THE INDIVIDUAL OPERATOR. FURTHER, QUANTITATIVE ASSESSMENT OF CARDIAC FUNCTION FROM ECHOCARDIOGRAPHY IS DIFFICULT AND THE TECHNIQUE IS QUITE UNSUITABLE FOR RECORDING DATA DURING EXERCISE (Matsumoto et al, 1982). IN A SIGNIFICANT NUMBER OF PATIENTS GOOD QUALITY ECHOCARDIOGRAPHS CANNOT BE OBTAINED FOR TECHNICAL REASONS.

Radio-isotopic techniques have been developed over recent years in an attempt to find a reproducible quantifiable non-invasive method of assessing cardiac function. The first experiments were carried out by Blumgart and Weiss (1927) who assessed pulmonary transit time of isotopes injected into the venous system. In 1948 Prinzmetal used more sophisticated Geiger counters to measure the passage of isotope through the right and left ventricles and 10 years later MacIntyre and his co-workers (1958) were able to estimate cardiac output from the isotope dilution curve derived from passage of a bolus injection to radionuclide through the heart. Since then there have been major developments in both isotopes and scintillation...
cameras such that dynamic imaging of the heart and calculation of cardiac volumes has become possible (Rowlands et al, 1981).

Full accounts of the methodology, advantages and disadvantages of radionuclide cardiac studies have already been published (Marshall et al, 1977; Dewhurst, 1981; Maseri and Vasile, 1984) and only those aspects relevant to the studies described in this thesis will be considered here.

**Isotopes**

Technetium\(^{99m}\) (\(^{99m}\)Tc) has become the most widely used radio-isotope in nuclear cardiac imaging and has been used in all the studies in this thesis. It is an artificially produced element which can be separated from its parent molybdenum\(^{99m}\) using a simple generator system (Richards, 1966). It has a half-life of about 6 hours and decays emitting a single gamma photon of 140 keV. This energy is sufficient to traverse tissues and is suitable for detection by the sodium iodide crystal of modern gamma cameras. For studies of the circulation it can easily be combined to either human serum albumin or red blood cells such that it is confined to the intravascular space. A method of electrolytically labelling human serum albumin with Technetium\(^{99m}\) has been developed in this laboratory (Millar et al, 1979). For longer studies leak of albumin from the circulation makes it necessary to use a Technetium labelled red cell preparation and for this we used a modification of the method described by Callaghan and his colleagues (1982) after demonstrating good labelling of the red cells and retention of the isotope within the
circulation (Millar et al, 1983, fig 1). The radiation dose of an adequate amount of tracer for radionuclide cardiography (700 MBq $^{99m}$Tc) is about 400 m Rad. per patient study.
Fig 1 Clearance of $^{99m}$Tc labelled red blood cells from the circulation after in vitro labelling ($n = 10$).
The single crystal gamma camera has been developed to provide images from patients after the injection of appropriate radiopharmaceuticals. Gamma photons are detected by a single sodium iodide crystal after passing through a lead collimator which excludes those rays which are not parallel to the axis of the camera. The crystal produces a light flash which is then detected by the photomultiplier tubes (between 20 and 100) positioned behind the crystal and its position on the x and y axis is recorded. The flashes produced by gamma photons within the required energy range (which is determined by the isotope used) are then displayed on a cathode ray oscilloscope and can be further processed by a computer (fig 2). In this way information about the distribution of injected materials can be studied. From the point of view of the heart, for example, $^{99m}$Tc pyrophosphate is taken up by and can be used to image areas of infarcted myocardium and Thalium$^{201}$ which behaves in a similar manner to potassium will show up ischaemic areas in the myocardium as an area of low uptake. Greatest use of the gamma camera for imaging the circulation including the heart following labelling of the blood is potentially made by linking the camera to a microcomputer system using "analogue to digital" convertors (ADC) such that quantifiable images of the heart can be constructed from the detected isotope counts. Using this methodology, two types of data collection are possible; the so-called first pass and gated equilibrium studies.
Patient positioned beneath single crystal gamma camera. The emitted -rays travelling parallel to the camera pass through the collimator, are detected by the sodium iodide crystal and the emitted light is amplified by the photomultipliers. Computerisation allows temporal and spatial analysis. Through analogue to digital convertors (ADC) the radioactive emissions from the heart can be stored and displayed as images on a grey scale. Interface with the ECG allows images to be constructed throughout the cardiac cycle.
The first pass method
The first pass method depends upon using the computer to present the isotope counts being detected by the gamma camera so as to visualise the passage of an intravascular isotope bolus through the right or left ventricle by collecting the isotope counts from the heart every 500 msec or so for several heart beats. After correction for the background activity, (which will obviously be low using this technique) the left ventricular ejection fraction (stroke volume/end diastolic volume) can be calculated from the fluctuations in isotope activity in the ventricle over a few cardiac cycles; the difference between the peaks and troughs being the ejection fraction. Such measurements of left ventricular function have been shown to correlate reasonably well with high tone contrast angiography (Schelbet et al, 1975). However, the count rates are relatively low and the procedure can only be carried out once. Further very fast collection periods which reduce the isotope count rates are required so that the peaks and troughs are not damped. Such damping causes underestimation of ejection fraction (Muir et al, 1977).

The technique allows calculation of cardiac output using the indicator dilution principle (Stewart, 1921) as first demonstrated by MacIntyre and his colleagues (1958) (fig 3). The area under the isotope dilution curve of passage of the intravascular isotope bolus through the right (or left) ventricle is unfortunately affected by recirculation of the radiopharmaceutical and variable background activity as the isotope passes through the pulmonary circulation. There are several further potential sources of error: firstly the low
An indicator dilution curve from the left ventricle detected by the gamma camera. The area (A), corresponding to the initial passage of radionuclide through the ventricle, is obtained from the gamma variate fit (solid line) to the data between approximately 20% of the peak height on the upslope and 50% of the peak height on the downslope. The equilibrium height (h) is the average count 8 min post injection.
isotope count rate allowed with this type of data collection means that delineation of the ventricular outline (and therefore quantification of the ventricular function) may be inaccurate; secondly the calculation of cardiac output is critically dependent upon curve fitting to the ventricular isotope peak to calculate the area, conventionally using a gamma variate fit (fig 3) and finally the blood volume must be accurately known. However, using a good bolus injection (which does not traverse the field of the heart) several groups have shown that cardiac output can be estimated using this technique (Alazraki et al, 1975; Hannan et al, 1980).

The gated equilibrium method
Using the gated equilibrium technique the left ventricular ejection fraction can be determined after the equilibration of isotope in the circulation (Strauss et al, 1971; Muir et al, 1977). By using the R wave of the electrocardiogram as a marker of end diastole, data can be collected in short time periods (frames) up to the next R wave. The information from a large number of heart beats or R-R intervals (conventionally around 500) can be combined to allow large numbers of counts to be collected, so improving statistical accuracy, assuming that the R-R interval is constant. A series of images is taken throughout the cardiac cycle over many beats and then by displaying the sequence of these images a cine representation of myocardial contraction can be derived (fig 4). Further the count rate from the left ventricle in any frame of such a cine representation is proportional to the amount of blood in the ventricle as long as there is no overlap of the cardiac chambers (fig 5). The separation of
The end-diastolic frame of the cine representation of ventricular contraction allowing delineation of the left ventricle. The left ventricle will lie within this region throughout the cardiac cycle. There is no significant overlap of other cardiac chambers using the $30^\circ$ left anterior oblique projection.
Fig 5 The count-time curve for the left ventricular region shown throughout the cardiac cycle with each point representing a frame. The counts are summated from each cardiac beat, using the electrocardiogram as a time marker. The background activity derived from extracardiac structures, which must be subtracted to derive the left ventricular counts is also shown.
the left and right ventricle is best achieved by visualisation from the left anterior oblique projection. From this the left ventricular ejection fraction (LVEF) can be determined as the difference between end diastolic counts (EDC) and the end systolic counts (ESC) divided by the end diastolic counts after a background subtraction (b) to allow for the isotope counts derived from the isotope within the lungs and other extra-cardiac structures has been made.

\[
\text{LVEF} = \frac{\text{EDC} - \text{ESC}}{\text{EDC} - b}
\]

The background correction is critically important because of the large contribution it makes to the count rate and is discussed further below.

This determination of LVEF is now widely used in the management of patients with cardiac disease as an assessment of left ventricular function and has been shown to correlate well with the development of heart failure and prognosis after myocardial infarction (Dewhurst et al, 1981). Others have questioned the value of LVEF in predicting prognosis claiming that the rise in systolic blood pressure on exercise is superior (Fioretti et al, 1984). Hence the precise role of this investigation in patient assessment is not clear.

Although radionuclide LVEF is a widely used measurement of ventricular function clinically, there has been relatively little
attention paid to the measurement of other parameters of cardiac function. Unfortunately ejection fraction expresses only a relative change in volume of the ventricle during the cardiac cycle as neither the end systolic nor the end diastolic volume are measured. Changes in ejection fraction during, for example, pharmacological intervention give little useful information as there may be changes in end diastolic volume which would, of course, be unknown. Further ejection fraction will be affected both by loading conditions of the ventricle and changes in inotropic state.

Hannan and co-workers (1980) derived the cardiac volume from repeated gated equilibrium studies using the indicator dilution of an isotope bolus passing through the heart with the "first pass" method to calculate the cardiac output (Alazraki et al, 1975). However, such methods have not been used very widely in clinical practice. They require good isotopic labelling to ensure the marker stays in the circulation, a good bolus injection and extreme care to ensure good images of the left ventricle are obtained. Further, blood sampling is required to calculate blood volume from isotope dilution and to allow appropriate correction for isotope delay and clearance. They do, however, have the advantage that no assumptions are required about the shape of the left ventricle such as are used in deriving ventricular volume from contrast angiography or echocardiography. In the context of ischaemic heart disease or other situations where the ventricles may not be the prolate ellipsoid, which is usually assumed, or contract uniformly, this may have particular advantage.
RADIO-ISOTOPE STUDIES OF RIGHT VENTRICULAR FUNCTION

In recent years there has been increasing interest in the use of radio-isotopes for studying right ventricular function. This is because the complex geometry and very variable shape of the right ventricle makes conventional contrast angiography unsuitable. It is also difficult to obtain echocardiographic pictures of the right ventricle and again assumptions need to be made about the shape of the ventricle which severely limits the accuracy of this technique particularly in patients with right ventricular dysfunction (Weitzenblum et al, 1983, Rodrigues et al, 1986). Very recently a complicated method confined to diastolic measurements has been outlined and this underlines the difficulties of analysis even of normal ventricles (Foale et al, 1986).

Although radionuclide techniques do not rely on any assumptions about the shape of the right ventricle, it was thought that the overlap of the right ventricle and the right atrium would prevent radionuclide determination of right ventricular ejection fraction (RVEF). However, Maddahi and colleagues (1979) suggested that by use of techniques defining the right ventricle both at end systole and end diastole, this could be overcome. This method was further refined by Xue and co-workers (1983) who improved the method of outlining the right ventricle using a sophisticated edge detection method based on phase analysis of the individual picture cell elements ("pixels") of the matrix making up the cardiac image (fig 6). They were also able to show that reproducible measurements could be obtained with
Amplitude (a) and Phase (b) analysis of the pixels within the left and right (outlined) ventricles derived from the volume time curve of each pixel. The left and right ventricles are clearly outlined and separated from the atria.
equilibrium blood pool scintigraphy. Radionuclide right ventricular ejection fraction, however, has not been shown to correlate with right heart failure or have the prognostic significance in cor pulmonale (MacNee et al, 1985) which was initially hoped (Brent et al, 1982). Again the measurement is affected by the pulmonary artery pressure and pulmonary vascular resistance but it does not help to distinguish between changes in right ventricular contractility and changes in pulmonary vascular tone. The clinical value of the estimation of right ventricular ejection fraction has not been determined as it has not been shown to affect management but it does allow calculation of the right ventricular volumes independent of the geometry. The combined use of invasive pulmonary pressure monitoring with radionuclide measurement of right ventricular volumes (to overcome the problems of right ventricular geometry) should allow differentiation between myocardial contractility and the effects of changing the afterload in the pulmonary circulation, as has been shown for the left ventricle (Sagawa et al, 1977; Miller et al, 1981). In this thesis a study of this methodology is described.
BACKGROUND CORRECTIONS FOR RADIONUCLIDE VENTRICULOGRAPHY

The isotope counts used to calculate ejection fraction and ventricular volume should be derived solely from the ventricle. Unfortunately in practice the gamma camera will also detect counts arising from non-cardiac structures, notably the lungs, which are in the field of view. In order to allow for this a background correction has to be made and such correction have been derived empirically from comparison with independent techniques (Marshall et al, 1977). It is important to realise that no method of background correction is perfect and that the purpose of the correction is to produce a correction factor such that radionuclide measurements consistently agree with independent determinations of cardiac function. In general background measurements from areas which lie immediately outside the ventricle have proved the most suitable as they produce results which are comparable with non-radionuclide techniques. In gated equilibrium studies where the background counts will be relatively high, changes in the regions from which background is derived do not markedly affect the final result as long as they are outwith the heart and great vessels (Marshall et al, 1977).

For first pass studies, the major problem is that background counts vary as the isotope bolus passes through the lung and recirculates during the study. Correction must therefore be made on a frame to frame basis. Uniformity of background counts is less reliable than at equilibrium and changes in the background region selected makes a
considerable difference to both the area under the ventricular isotope dilution curve and the magnitude (height) of the equilibrium count rate (Hannan et al, 1980). Small changes in these values can produce large variations in the calculated cardiac output (see fig 3). The only satisfactory way to determine which type of background correction is most appropriate for any given imaging system is to confirm that the data obtained is reproducible and compare the results with those derived from an independent technique.
STUDY OF THE PERIPHERAL CIRCULATION

Many drugs used in the treatment of left and right heart failure and hypertension produce their cardiovascular effects by altering the peripheral circulation and produce only indirect effects on the heart. The arterial circulation has been well studied by monitoring blood pressure and using this along with cardiac output estimations, sometimes using a correction for central venous pressure to establish so-called peripheral or systemic vascular resistance (PVR).

\[ \text{PVR} = \frac{\text{mean arterial pressure} - \text{central venous pressure}}{\text{cardiac output}} \]

The venous system which contains 70% of the blood volume at any one point in time (Shepherd and Vanhoutte, 1979) has been studied far less, largely because of the technical difficulties (Robinson, 1978; Safar and London, 1985) which are particularly troublesome in patients who are unwell. However, it has been suggested that the venous system is particularly important in heart failure (Braunwald, 1981) and hypertension (Safar and London, 1985) because of the very considerable changes in the heart and circulation which can be brought about by altering the venous return to the heart.

Strain gauge plethysmography was devised by Whitney (1953) but because it is inaccurate and cumbersome, several workers have considered radionuclide methods. Clements and co-workers (1981) and Rutlen and colleagues (1981) have both used a gamma camera to examine
changes of an intravascular radio-isotope on the capacitance vessels of the calf using the principle that the isotope counts detected will be proportional to the blood volume in the area studied (in this case the legs) and that most of this blood will be in the venous system. Both groups were able to show a good correlation ($r = 0.71 - 0.95$) between the detected changes in radioisotopic counts in the legs and the volume changes measured by strain gauge plethysmography with varying degrees of venous occlusion. Unfortunately this method requires two gamma cameras in close proximity to each other if cardiac function is to be studied simultaneously and for this reason it has not been widely used. Development of a more suitable technique using the same principle, if sensitive enough, would allow easier non-invasive investigation of the effects of drugs on peripheral and central compartments of the circulation simultaneously (see Chapter 3).
CONCLUSIONS

Radionuclide study of the circulation offers a practical non-invasive alternative to conventional angiographic techniques and may be particularly suited to the simultaneous study of the heart and peripheral circulation. It also offers advantages of not relying on assumptions about the geometry of the cardiac chambers which may be of great benefit in studying patients with abnormal cardiac function and for assessment of the right ventricle.

For the pharmacological studies of the pulmonary and systemic circulation proposed, several preliminary validation developments and studies were required:

1. To ascertain the reproducibility of left ventricular end diastolic volume and ejection fraction measurements.
2. To ascertain the reproducibility of right ventricular ejection fraction and determine if this was stable over a period of 7 days to allow study of chronic drug therapy.
3. To confirm that cardiac output could be measured reliably by radionuclide methods and establish the best technique.
4. To develop a simple radionuclide technique for observing drug induced changes in the peripheral venous bed.
5. To obtain data in a normal population and to assess variability.
CHAPTER 3
INTRODUCTION

From the description of radionuclide methodology available for studying the circulation (chapter 2) and an appraisal of the requirements for simultaneous assessment of the effects of drugs on the heart, the arterial system and veins, it was apparent that the reproducibility of measurements needed to be ascertained such that the significance of any changes produced by pharmacological intervention could be evaluated. A satisfactory method for measuring cardiac output was needed. Further, it was necessary to ensure that the imaging system used for the studies had been validated by independent methodology. Finally, it was necessary to develop a suitable method based on the recently described radionuclide techniques for studying the effects of drugs on the peripheral veins.

In this chapter, studies to answer the following questions are described:

1. How reproducible are radionuclide gated equilibrium measurements of left and right ventricular ejection fraction?
2. Does right ventricular ejection fraction remain constant with time in patients with chronic bronchitis and emphysema?
3. How accurate are radionuclide measurements of cardiac volumes and cardiac output?
4. Can a peripheral radioisotope detector system detect changes in venous volume produced by drug intervention?

ETHICAL APPROVAL

All of the studies described in this thesis had the approval of our Institute's Ethical Committee and approval from the Administration of Radioactive Substances Advisory Committee (ARSAC). Where necessary clinical trial exemption certificates were obtained from the Committee on Safety of Medicines.
The reproducibility of radionuclide ventriculography is dependent upon accurate definition of the left and right ventricles at end-diastole. This becomes more important for the determination of changes in ventricular volumes than ejection fraction where inaccuracies in counts detected from the edge of the ventricle produce less error. It was therefore decided to carry out studies to test inter-observer and inter-study variability of both ventricles after the camera/computer system had been tested with a standard Vanderbilt cardiac phantom.

Patients
We selected 15 sequential patients with ischaemic heart disease who had been referred to the laboratory for radionuclide ventriculography as part of their clinical investigation for the left ventricular study and subsequently a further 12 patients for study of the right ventricle. All patients were clinically stable at the time of study.

Methods
Cardiac phantom study
The standard Vanderbilt cardiac phantom (Copintex Inc, Pittsburgh) was positioned in front of the gamma camera after being filled with water containing 80 MBq (2 mCi) of $^{99m}$Tc which had been well dispersed (figure 7). Images were collected with shields to simulate left ventricular ejection fractions of 0.25, 0.50 and 0.75.
Vanderbilt cardiac phantom filled with isotope and positioned in front of the gamma camera. The central part rotates synchronously with the simulated electrocardiogram to simulate left ventricular contraction and relaxation. A static chamber to simulate background activity is contained within the wall of the core opposite to the gamma camera.
The studies were carried out at rotation speeds to simulate heart rates of 70, 90 and 160 bpm using 20 msec collection periods throughout the simulated R-R cycle.

Clinical studies
All the patients were given an intravenous injection of 750 MBq (20 mCi) of technetium\textsuperscript{99m} electrolytically labelled to human serum albumin (Millar et al, 1980) into a vein in the right antecubital fossa. Minor modification of the position was sometimes required to achieve good separation of the left and right ventricles. Images were collected on a Searle LEM mobile gamma camera equipped with a high sensitivity parallel-hole collimator linked to a Cromemco System 3 microcomputer using a series of programmes designed in-house by Dr C Adie. This system has been designed to collect the data in frame mode and images from the composite cardiac cycle are then displayed on a television monitor. All studies in this thesis have been carried out using this imaging system which has been well documented (Muir et al, 1977; Hannan et al, 1980) and it will not be further described. I used manual edge detection methods to outline the left ventricle and to improve accuracy, volume-time curves of the picture cell elements (pixel) around the edge of the ventricle were studied individually to establish whether they were inside the left ventricular region or not. Clearly pixels of regions showing a ventricular time curve with a fall in end systolic counts were inside the ventricle whereas those with no changes throughout the cardiac cycle were deemed outside the region of the left ventricle. A region was selected immediately lateral to the left ventricular
border to make the background correction. We also used a programme
designed in the department by Dr Adie which carried out Fourier
analysis of the ventricular time curves of each pixel (Links et al,
1980) to automatically determine the edge of the ventricle; so-called
'phase analysis' (see fig 6). Each patient was studied for 500
cardiac beats twice with the second study commencing immediately on
completion of the first. Reproducibility of right ventricular
ejection fraction was carried out in the same manner using the
Fourier analysis to help identify the outline of the right ventricle
and with subtraction of the region outlining the right atrium at end-
systole as described by Xue et al (1983). A background region was
identified adjacent to the inferior border of the right ventricle.
The data was analysed independently and blind by myself and Dr W J
Hannan.

RESULTS

Cardiac phantom study
The results are shown for the low (0.25), medium (0.50) and high
(0.75) shields in table 1. The high readings are comparable with
other studies (Tonge et al, 1986; see table 1) when care has been
taken to use short collection periods (< 20 msec) to avoid missing
the peaks and troughs of the isotope count curve.
CLINICAL STUDIES

Left ventricular ejection fraction estimation
The individual data for the 15 patients is shown in table 2. The left ventricular ejection fraction (LVEF) showed very good inter-study (mean difference 0.02), inter-observer (mean difference 0.01) agreement (fig 8). The use of phase analysis is extremely time consuming and did not appreciably improve edge detection and has therefore not been used for outlining the left ventricular region for the purpose of the following studies. The left ventricular end-diastolic counts (corrected for background, decay and inotropic clearance) showed similarly good reproducibility (table 2).

Right ventricular ejection fraction estimation
In 12 patients with chronic obstructive lung disease (COLD) the RVF was 0.35 ± 0.13 and there was little inter-study variation (mean difference 0.03) (fig 9). Inter-observer agreement was confirmed with 3 of the studies (difference < 0.02).
Fig 8  Inter operator and inter study variation of left ventricular ejection fraction in 15 patients.
Inter study variation of right ventricular ejection fraction in 12 patients with chronic obstructive lung disease studied twice, 30 minutes apart.
REPRODUCIBILITY OF RIGHT VENTRICULAR EJECTION FRACTION MEASUREMENTS OVER TIME

Previously reproducibility of radionuclide RVEF has only been determined over short periods as above (Maddahi et al, 1979; Xue et al, 1983) and it has been suggested that the measurement might not be reproducible over several days (Sadoul P, personal communication). This would clearly have implications for studies of chronic drug therapy and so the measurement was carried out in a group of stable patients on two occasions, 7 days apart.

Patients

Twelve patients with stable chronic obstructive lung disease, as determined by body weight, pulmonary function tests (FEV₁/FVC), pulse, blood pressure and clinical examination were studied. None had clinical evidence of tricuspid incompetence or other valvular heart lesions.

Methods

Gated radionuclide ventriculography was carried out, as described above, twice, seven days apart, along with the measurements listed above to confirm the clinical state of the patients was stable (variation < 10%) over the week between the two studies.
RESULTS

The individual data is given in tables 3 and 4.

The group mean values for left and right ventricular ejection fraction were not changed (see fig 10) and the reproducibility of LVEF was very good (mean change = 0.03 range 0 - 0.04). In any one individual the reproducibility of LVEF was similar to the study above. However, there was considerable variation between the RVEF determinations in any individual over the 7 days between the two estimations (mean change = 0.07 range 0.01 - 0.18, fig 10).
Fig 10  Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) in 12 patients with stable chronic obstructive lung disease measured one week apart. There is no significant change in the mean values but the individual variation in RVEF is considerable (mean difference 0.07).
VALIDATION OF CARDIAC OUTPUT ESTIMATIONS

In the first study I decided to compare two radionuclide techniques for determination of left ventricular volumes and cardiac output in an attempt to determine the most satisfactory method which could then be validated against an independent technique. We compared the first pass method described by Hannan et al (1980) in this laboratory with a modification of the background correction (because corrections used previously have led to a variable underestimation of the cardiac output), and the gated equilibrium method described by Links et al (1982).

FIRST PASS METHOD

This uses the principle of radioisotope dilution based on the Stuart Hamilton equation (Stuart, 1921; Hamilton, 1928) as described in chapter 2. A Viggo Venflon catheter was placed in a large medial anticubital vein in the right forearm and connected to a normal saline infusion drip. The infusion was sited so that a high flow could be produced. A further Venflon catheter with three-way tap was then placed in the opposite anticubital fossa for sampling of blood. The gamma camera was positioned over the patient as described above. Accurate positioning was essential to obtain the isotope dilution curve for the left ventricle and this was achieved by placing the liquid flood source of 200 MBq of technetium$^{99m}$ dispersed in water behind the patient in the same plane as the gamma camera. The shadow produced by the heart could be easily detected
and used to position the camera accurately. The gamma camera was connected to a Cromenco System 3 microcomputer programmed to make 500 msec collection periods of isotope counts for a total of 40 seconds and then a further frame when equilibrium had been reached after 8 minutes. This time for equilibrium had been established by studying the count rates over the legs for periods of up to 10 minutes after such a bolus injection and showing that equilibrium was reached after about 5 minutes (by which time there was no further change in count rate). Cardiac output was then calculated from the corrected area under the curve (see chapter 2) using a background region 2 pixels outside the border of the left ventricle and the blood volume (fig 3). The blood volume was calculated from dilution of the isotope bolus in the standard manner (Millar et al, 1979).

**Gated Equilibrium Method**

A dose of isotope was injected into the circulation in the form of technetium$^{99m}$ labelled to human serum albumin as described previously and allowed to equilibrate for 8 minutes. Blood sampling to allow for clearance of isotope was undertaken as above. At this point a standard gated equilibrium radionuclide ventriculography was carried out for 500 heart beats in the same position as above. During the middle of the study 20 ml of blood was taken from the left arm and placed in a container. This was then counted for known time after the patient's study using the same gamma camera so that the count rate for 20 ml of blood could be calculated. The distance from the heart to the gamma camera was calculated as described by Links et al
(1982) using point sources positioned on the anterior chest wall of the patient following the gated equilibrium study. From static images taken in 30° left anterior oblique and anterior projections the distance between the gamma camera and the centre of the left ventricle could be calculated (fig 11). In this way an attenuation factor to calibrate the left ventricular end-diastolic counts against the counts in the 20 ml blood sample could be made and the cardiac output (CO) calculated.

\[ CO = \text{Heart rate} \times \text{LVEF} \times \text{end-diastolic volume} \]

**PROTOCOL**

Ten patients were studied by both methods. The first pass cardiac output method was carried out first in all cases and immediately followed by a gated equilibrium study. From the results determination of the cardiac output and heart rate, stroke volume and therefore left ventricular end-diastolic volume were calculated.

**RESULTS**

The results of the individual data for cardiac output is shown in table 5. In one patient the gated equilibrium method gave exceedingly high values for end-diastolic volume (556 ml) and cardiac output (17.7 l). The patient was obese but the estimated attenuation factor appeared disproportionately large, so increasing the calculated absolute left ventricular volumes. Removal of this
Point source \( (p) \) positioned in centre of LV as seen by gamma camera

(A) Depth of center of left ventricle \( (d) \) along the left anterior oblique axis.

(B) Projection of \( d \) in anterior view \( (d') \)

(C) Calculation of \( d \) from \( d' \)

\[
def = \frac{d'}{\sin 30°}
\]

Fig 11 Method of calculating distance between centre of left ventricle and gamma camera (modified from Links et al, 1982).
patient's data from the analysis improves the agreement between the two methods of measurement. Overall, however, it can be seen that there was a reasonable correlation in left ventricular end-diastolic volume \((r = 0.93, \ p < 0.01)\) and cardiac output \((r = 0.71, \ p < 0.05,\) fig 12). However, this correlation conceals a consistently lower value from the gated method (Bland and Altman, 1986). Using the gated equilibrium technique several of the cardiac output estimations were very low, even allowing for the degree of left ventricular failure in some of these patients, and surprisingly the left ventricular end-diastolic volume was also low in some of the patients with reduced left ventricular ejection fraction \(< 0.30\), and evidence of heart failure (see table 5).
Fig 12 Comparison of first pass and gated equilibrium methods for determining left ventricular end diastolic volume (EDV) and cardiac output (CO).
DISCUSSION

The first pass method was much easier to carry out and derive the cardiac output. It did not involve the use of correction factors to allow for the distance between the left ventricle to the gamma camera needed for the gated equilibrium method. Some of these corrections did not appear reasonable. In the large group of patients studied by Links et al (1982) there was a very good correlation between the gated radionuclide method and contrast angiography despite some radionuclide estimates differing by more than 30% with the angiographic measurements. Further, their patients (31 of 35) had ejection fractions of greater than 0.30, implying good left ventricular function. It seems likely that in such patients the left ventricle will be more clearly visualised and will be contacting synchronously so that error in defining the radioisotope counts will be less than in patients with heart failure. We therefore chose to compare the first pass method of assessing cardiac output for the comparison with thermodilution measurement with a view to validating it for the pharmacological studies proposed.
We were able to compare the first pass radionuclide measurement of cardiac output as described above with thermodilution in 6 patients. The cardiac output was determined by thermodilution using Swann Ganz type catheterisation of the pulmonary artery (Swan et al, 1970). In the catheter laboratory, the flow directed pulmonary artery catheter was passed into the pulmonary artery from a vein in the patient's arm using the standard Seldinger technique, and connected to a thermodilution cardiac output monitor (Instrumentation Laboratory, model IL602). Three measurements were taken by injection of 10 ml of cold saline at 4°C. The thermal dilution measurement was immediately followed by the first pass radionuclide assessment of cardiac output using a 700 MBq bolus of $^{99m}$Tc human serum albumin as described above. The results are shown in table 6 and indicate a good agreement between the two methods in the 6 patients studied (mean difference 0.57 l, thermodilution measurement = 1.07 x radionuclide measurement -0.79, $r = 0.94$, $p < 0.02$).
DISCUSSION

Radioisotope studies allow non-invasive study of the circulation with a minimum of discomfort to the subject so that repeated studies can be undertaken if measures are adopted to keep the isotope dosage to a safe minimum. Using these radionuclide methods, it is reasonable to study patients with mild disease and normal subjects.

Ejection fraction measurements

It is important to establish the reproducibility of the techniques being used to measure ejection fraction because the measurements are to a degree observer-dependent and will vary from laboratory to laboratory. This data for our laboratory is given in the results above. For the left ventricle the good reproducibility is comparable to other studies (see Iskandrian, 1987) and is in agreement with previous data from this laboratory using earlier methodology (Muir et al, 1977). Less data is available for the reproducibility of right ventricular ejection fraction measurements using the gated equilibrium technique (Maddahi et al, 1979) but Xue and co-workers (1983) in our laboratory showed good inter-observer and inter-study reproducibility of right ventricular ejection fraction when the studies were carried out within 30 minutes of each other. They paid considerable attention to definition of the right ventricular outline using phase analysis and were careful to make a correction to allow for the right atrium overlapping the region containing the right ventricle at end-systole. Using the same technique but a different computer system for analysis of the images, similar reproducibility
was obtained in the study described above. This confirms that gated equilibrium determination of right ventricular ejection fraction is practicable for short studies, and would be appropriate for studies of drug intervention.

Using conventional techniques determination of changes in right ventricular volume is difficult because of the variable geometry and difficulty in visualising the cavity (Xue et al, 1983). Hence radioisotope techniques which are not dependent upon the geometry of the ventricle provide a useful way of studying right ventricular failure. Further, if cardiac output and pulmonary artery pressure are measured simultaneously using a pulmonary artery Swan-Ganz type catheter (Swan et al, 1970), the pressure/volume curves for the right ventricle could be calculated. Sagawa et al (1977) have shown that the end-systolic pressure/volume analysis for the left ventricle is independent of afterload conditions of the left ventricle but sensitive to changes in inotropic state. Such argument should also hold for the right ventricle as discussed in chapter 5 and allow assessment of the inotropic state of the right ventricle.

Right ventricular ejection fraction (RVEF) will be dependent upon afterload and therefore the factors which affect pulmonary vascular resistance. To establish whether the measurement of RVEF could be used to assess the chronic effects of drugs on the right ventricle and pulmonary circulation, it was necessary to study the RVEF over time in a group of patients with chronic bronchitis to establish how much it varies independent of any intervention. The above study
confirms that left ventricular ejection fraction is very reproducible over the period of 1 week in stable patients (mean change 0.03) but right ventricular ejection fraction was not so reproducible (mean change 0.07). Whilst the mean RVEF of the group was unchanged, there was marked variation in any individual patient (0.01 - 0.18). This suggests that even in stable patients factors which are known to affect the pulmonary circulation may change. RVEF is dependent upon afterload and factors which affect pulmonary vascular tone, for example, the alveolar oxygen concentration, may not be constant. This may be particularly true in patients with chronic bronchitis. From the available data, further analysis of this problem is not possible. However, studies which use RVEF measurements over periods of more than a few hours would need to contain sufficient numbers of patients and be appropriately designed to allow any effect of a drug intervention to be differentiated from underlying variability. For the purposes of my studies on the effects of drugs on the right ventricle, it was decided that radioisotope techniques available for assessment of the right ventricle were not appropriate for chronic studies. This observation underlines the importance of including a suitable control group in the design of pharmacological studies to establish a baseline against which changes produced by therapeutic intervention can be assessed.

Cardiac output determination
The determination of blood flow or cardiac output is fundamental to study of the circulation. A reliable non-invasive method of determining cardiac output or changes in cardiac output represents a
significant advance over invasive technology which has significant morbidity limiting its use. Radioisotope techniques meet these criteria. Unfortunately the radionuclide determinations inevitably involve several assumptions and approximations; notably correction for background counts from extra cardiac structures. This background activity arises primarily from three sources, the pulmonary vascular bed, scatter from the ventricle not being studied, and scatter from the atria (chapter 2). The corrections applied are empirical and can only be determined by comparison with other techniques of proven reproducibility. Hence it was necessary to establish a satisfactory method in our laboratory and compare this with the invasive thermodilution technique in a group of patients to show that accurate measurement of cardiac output was being obtained from the radio-isotope studies.

For studies of drug intervention, the calculation of absolute cardiac output is less critical and changes in cardiac output may provide sufficient information about the effects of a particular intervention. Using radionuclide ventriculography this is technically much easier as the background corrected isotope counts arising from the left or right ventricle will be directly proportional to the ventricular volume so that if the clearance of the isotope from the circulation and its physical decay are known, several studies from the same patient taken at any one time can be compared. Using the heart rate recorded from the studies (HR₁ and HR₂), change in cardiac output (Δ CO) can be calculated from the background and decay corrected end-diastolic counts (EDC₁ and EDC₂)
and the left ventricular ejection fractions ($LVEF_1$ and $LVEF_2$).

$$\Delta CO = [HR_2 \times LVEF_2 \times EDC_2] - [HR_1 \times LVEF_1 \times EDC_1]$$

In summary it has been possible to demonstrate that $LVEF$ and $RVEF$ can be measured reproducibly but that $RVEF$ is not constant with time in patients with chronic bronchitis. Also cardiac output and changes in cardiac volumes can be determined non-invasively such that radioisotope study of the heart in intact man is feasible.
DEVELOPMENT OF A RADIONUCLIDE SYSTEM TO DETECT CHANGES IN VENOUS VOLUME

From the previous discussion (chapter 1) it is clear that the effects of drugs on peripheral veins are important.

The dilating effects of nitrates on veins are well established (Franciosa et al, 1978) as discussed in chapter 1 and it seemed appropriate to use glycercyl trinitrate (GTN) to test whether a simple nucleonics device could detect the increased volume of blood in the peripheral veins which is produced by nitrates. Further it was proposed to test the specificity of this technique to venous dilation by contrasting the responses with the arteriolar vasodilator hydralazine (Franciosa et al, 1977) which appears to be devoid of any action on veins (Ablad, 1963).

A study was therefore designed to simultaneously assess the effects of glycercyl trinitrate and hydralazine on the arterial and venous system in a group of patients. As part of this study the effect of increasing calf venous blood volume with a thigh pressure occlusion cuff were also studied.

EFFECTS OF HYDRAZINE AND GLYCERYL TRINITRATE ON THE ARTERIAL AND VENOUS CIRCULATION IN ISCHAEMIC HEART DISEASE

Patients

Twenty two patients with ischaemic heart disease who had been
referred for radionuclide ventriculography were studied. None were
taking beta-adrenoreceptor antagonists or calcium channel blockers
and no patient had received glyceryl trinitrate or similar
preparation for 6 hours prior to the study.

In 6 patients no drug was given so that baseline assessments and
intravascular retention of the isotope could be observed for a
similar period to the pharmacological study. An assessment of
changes in calf volume was made using stepwise increase of pressure
on the veins alone with a large thigh blood pressure cuff in another
group of 6 patients.

Ten patients were randomised into two equal groups, the first being
given glyceryl trinitrate after the control measurements followed by
hydralazine and the other group being given hydralazine initially
followed by glyceryl trinitrate.

METHODS

The patients were studied resting supine in a room at 22°C and
measurements commenced after an initial rest period of 15 minutes.
Heart rate was monitored continuously with an ECG recording and blood
pressure was measured by an independent observer using conventional
sphygmomanometry (diastolic phase 5). Mean arterial blood pressure
was calculated from the diastolic pressure plus one third of the
pulse pressure. Standard ECG gated equilibrium blood pool
ventriculography was carried out after an intravenous injection of
750 MBq Technetium$^{99m}$ electrolytically labelled to human serum albumin had been injected into the right forearm and given 8 minutes to equilibrate in the circulation (fig 13). From this data left ventricular ejection fraction was calculated and changes in end-diastolic volume, stroke volume and therefore cardiac output were calculated. Peripheral vascular resistance was expressed as the mean arterial pressure divided by the change in cardiac output relative to the baseline recordings.

Changes in the peripheral vascular volume or venous counts were measured with a simple scintillation detector. This was made from a 4 cm diameter x 2 cm sodium iodide crystal coupled to a 5 cm diameter photomultiplier and positioned within a 6 cm internal diameter brass collimator. This detector was then connected to a portable nucleonic system (Alrad Instruments Limited, model MS 310E) and a printer to record minute counts (Datac Limited, model 412L). Because a relatively high activity of technetium$^{99m}$ was required for the simultaneous gamma camera measurements, sensitivity of the scintillation probe was reduced by positioning the probe 15 cm above the patient's calf within the brass collimator. This position gave a uniform response across the patient's calf and prevented any change in detected isotope counts from small movements by the patient. In addition, the patient's ankle was held steady using bean bags and the leg being studied was shielded from the other leg with a lead screen. In three patients the counts recorded with this device were compared with those obtained from the opposite leg simultaneously when measured by the gamma camera.
Fig 13  Relative activity of $^{99m}$Tc in blood after IV administration of human serum albumin. Each point is the mean value for 6 patients, after correcting for physical decay. Standard errors for any point were less than 5%.
STUDY PERIODS

Venous Compliance study
For the measurement of changes in compliance a thigh blood pressure cuff was placed around the calf proximal to the detection device described above and after 3 minutes of baseline recording, the blood pressure cuff was pumped up to 10 mmHg for 3 minutes, then 20 mmHg, 30 mmHg, 40 mmHg, 50 mmHg, 60 mmHg at 3 minute intervals. The first minute of collecting during which the accumulation of blood occurred was discarded and the data from the final 2 minutes was used. After 3 minutes at 60 mmHg the pressure cuff was deflated and a new baseline was recorded. In the second group of patients, calf counts were just recorded continuously without any intervention for a period of 1 hour with 1 ml samples of blood being taken at about approximately 10 minute intervals to allow measurement of the retention of the isotope within the circulation.

Drug study
Heart rate and peripheral venous counts were measured continuously and blood pressure was recorded every 2 minutes. Radionuclide ventriculography was carried out in the control period and over the peak effect of the drugs, that is approximately 3 minutes after giving 0.5 mg of GTN sublingually and 10 minutes after the intravenous injection of hydralazine. A 20 minute period of stabilisation was allowed between the two drugs. The collection period for each ventriculogram was approximately 6 minutes.
RESULTS

Preliminary observations
Where no pharmacological agent was administered the decay corrected counts from the calf were less than \( \pm 2\% \) once initial equilibrium had been achieved. There must have been some biological clearance in correction for this using the venous blood sample suggested there was indeed an increase of 8\% of counts in the calf per hour. This probably represents a slight leakage of technetium from the vessels into the calf over this period of time. In the three patients in whom counts were measured simultaneously with the simple scintillation detector and the gamma camera, the changes in count rate were identical.

In those 6 patients in whom stepwise increase in pressure was applied to the calf by the blood pressure cuff, a stepwise increase in count rate was detected in the calf with the increasing inflation pressures (fig 14). The count rate returned to baseline with deflation of the cuff.

Pharmacological studies
In each case the administration of GTN produced similar changes (fig 15). The mean changes for the group are summarised in figures 16 and 17 and listed in table 7. Heart rate rose by 10.8 \( \pm 2.3 \) (SEM) bpm (\( p < 0.001 \)), systolic blood pressure fell by 5.5 \( \pm 2.5 \) mmHg (\( p < 0.05 \)). There was no significant change in diastolic BP. Left
Fig 14  Decay corrected isotope count rates (± SEM) over the calf in 6 patients with progressive increase in the pressure of a thigh pressure cuff from 0 to 50 mmHg, followed by deflation of the cuff.
Fig 15  Isotope counts detected over calf in a patient given hydralazine (H) followed by glyceryl trinitrate (G).
Fig 16 Change in left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and cardiac output (CO) in 10 patients (± SEM) following the administration of glyceryl trinitrate (GTN) and hydralazine.
Fig 17  Change in systemic vascular resistance (SVR) and venous counts detected from the calf with glyceryl trinitrate and hydralazine in 10 patients (± SEM).
ventricular ejection fraction increased by $0.034 + 0.007$ (p < 0.001) and end-diastolic volume fell by $14.6 + 4.5\%$ (p < 0.005). Stroke volume (-4.9 + 5% NS) and cardiac output (+7.8 + 5.3% NS) were not significantly changed. The calculated systemic vascular resistance fell by $10 + 5.4\%$ (p < 0.05). There was an associated increase in the calf counts of $9.6 + 1.5\%$ (p < 0.005).

In contrast, after hydralazine heart rate increased by $5.2 + 1.3$ bpm (p < 0.005) and systolic blood pressure fell by $12.5 + 1.5$ mmHg (p < 0.001), with diastolic blood pressure falling $8.0 + 1.3$ mmHg (p < 0.01). End-diastolic volume was reduced $6 + 2.7\%$ (p < 0.05) and ejection fraction rose by $0.058 + 0.010$ (p < 0.001). Stroke volume rose by $9 + 3.7\%$ (p < 0.05) and cardiac output increased by $16.4 + 4.4\%$ (p < 0.005). Calculated systemic vascular resistance fell by $18.9 + 3.8\%$ (p < 0.001). Calf count rates were little changed (-2 + 2.6%, NS).
Acute studies of vasodilators in left heart failure

The radioisotopic technique designed to look at changes in peripheral vascular volume showed clear and reproducible differences between the glyceryl trinitrate and hydralazine. The effect of nitrates on the peripheral venous bed is probably very important. Approximately 70% of the blood volume is in the venous side of the circulation (Shepherd and Vanhoutte, 1979) and there is no reason to suspect that this situation does not pertain to the calf. Measurement of radioactivity within the blood pool from this region must to a large extent reflect venous capacitance assuming that the isotope marker remains within the circulation. We have shown that this is true for the time course of these studies using the electrolytic method of labelling $^{99m}$Tc to albumin (Millar et al, 1979). The comparison of blood pool imaging using a gamma camera with standard plethysmographic techniques simultaneously using both arms has shown a good correlation (Rutlen et al, 1981). I was unable to make a direct comparison of the radionuclide method with strain-gauge plethysmography (Whitney, 1953) but it was my intention to develop a technique which was sensitive to the effects of drugs on the peripheral venous system. I have shown that producing occlusion of the veins of the leg with a large sphygmomanometer cuff, produces stepwise increase in calf counts at levels of pressure which would not materially affect arterial blood flow. Further, the readings at different occlusion pressures quickly stabilise (less than one minute). The fact that hydralazine did not have any effect on the
calf counts despite obvious systemic effects on the arterial circulation further supports the view that the technique is sensitive to change in venous but not arterial tone. The mechanism of action of hydralazine on arterial tone is unclear. Several mechanisms including chelation of ions required for excitation-contaction coupling (Koch-Weser, 1976) and inhibition of dopamine conversion to noradrenaline (Songkittiguna et al, 1980) have been suggested. Worcel (1978) has demonstrated that even at high concentrations, hydralazine does not inhibit portal vein tone and Ablad (1963) demonstrated no change in venous volume of the forearm with hydralazine using standard plethysmography. Thus it seems that hydralazine does not have any effect on the venous bed. Hence this method allows distinction between changes in 'arteriolar' and 'venous' tone and will allow greater understanding of drugs acting on the cardiovascular system.

The effects of hydralazine and glyceryl trinitrate on the circulation in patients with left ventricular failure have assumed greater importance with the recent direction of therapy towards manipulating the vascular bed (Miller et al, 1982) and the very recent observations, discussed in chapter 1, that combined arteriolar and venous dilation might improve the prognosis of some patients with chronic left ventricular failure (Cohn et al, 1986). It will be important to assess newer vasodilators because it may be that compounds with an action on both the arterial and venous beds would prove useful in heart failure whilst arterial vasodilation may be more appropriate for the management of hypertension. It is
therefore most important to adequately evaluate drugs before clinical trials are mounted.
CHAPTER 4
NORMAL SUBJECT STUDIES

INTRODUCTION

Although radionuclide estimations of cardiac function are widely used, there is little data available for normal subjects (Iskandrian, 1987). In our own laboratory data is only available for patients presenting with atypical chest pain and in general the populations studied have been extracted from groups of patients attending hospital or patients who have had coronary artery disease treated by coronary artery bypass grafting. Further, there is no data available for a Scottish population, in whom the incidence of ischaemic heart disease is known to be higher than all other Western populations (Tunstall Pedoe et al, 1986). The effects of age and exercise on cardiac function in a normal population aged less than 65 years have not been well documented (Rodeheffer et al, 1984). It was therefore felt important to study a group of normal subjects who had not had any contact with a physician. For comparison a group of subjects with angina pectoris were also studied.

SUBJECTS

Normal subjects
A total of 60 men were studied. Fifty control men from a large case control study of angina in the community (Wood et al, 1987) were invited to take part in the radionuclide study after clinical examination with electrocardiography and the standard WHO chest pain
questionnaire (Rose et al, 1977) has excluded a history of angina pectoris, hypertension or overt ischaemic heart disease. Forty three patients agreed to the study. Their age ranged from 35 - 54 years with a mean of $43 \pm 5.7$ (SD) years.

In addition 17 younger men age 25 - 34 (mean $30 \pm 4.0$) years who were the husbands of insulin-dependent diabetic women were selected from the Diabetic Out-Patient Clinic of this hospital. All subjects agreed to the study which had the approval of the hospital Ethical Committee and ARSAC. A history was taken from each subject. They were given a clinical examination along with measurement of FEV$_1$, FVC and a standard cardiac exercise test using the Bruce protocol (Bruce et al, 1963). None of the subjects had diabetes or proteinuria. They all had normal blood pressures (see table 8) and 16 of the 17 men had normal electrocardiographs. One man had an abnormal electrocardiograph and exercise tolerance test and he has been excluded from the analysis (subject 17).

Hence a total of 60 normal men age 25 - 54 years were studied and the analysis was carried out on 59 subjects.

Angina subjects

Thirty six of 50 age-matched men with angina pectoris as determined by the standard WHO chest pain questionnaire (Rose et al, 1977) drawn from the same population study of 6,000 men (Wood et al, 1987) who agreed to the protocol were also studied. The ages of these 36 men ranged from 35 - 54 years with a mean of $43 \pm 6.3$ years. None had
any previous history of coronary heart disease and none were taking cardiovascular drugs.

**Protocol**

The radionuclide investigations were carried out with the operator (myself) blind to the subject's status. All of the subjects had a standard electrocardiographic exercise tolerance test using the Bruce protocol (Bruce et al, 1963).

The men attended the radionuclide laboratory after being weighed and lay down on the examination couch. An intravenous drip of saline was set up into a large vein on the medial side of the antecubital fossa in the right arm using a Venflon cannula attached to a fluid giving set with a rubber bung for injection of isotope. The camera was positioned over the subject. After an acclimatisation period first pass study for determination of cardiac output was carried out in the 17 men who had been recruited through the diabetic clinic. This was followed immediately by a gated equilibrium study as described above. The estimation of cardiac output by first pass isotope dilution was only made in this group. A gated equilibrium study was performed in all 60 normal subjects and the 36 subjects with angina. Sampling of peripheral blood was carried out to allow correction for clearance of the isotope in the circulation.

Finally using the supine exercise bicycle (Siemens Ergomed 740L) a further radionuclide ventriculogram was taken during steady
submaximal exercise at 75 watts after a constant heart rate had been achieved. (The first 20 subjects were initially exercised at 50 watts but less consistent data was obtained). From these studies, resting and exercise heart rate, left ventricular ejection fraction and cardiac output were measured. Using these data left ventricular end-systolic and diastolic volumes were calculated.
RESULTS

Normal young subject group (Age 25 - 34 years)
The individual subject data is shown in tables 8 and 9 and the mean for the group are summarised in table 8. All subjects had a resting left ventricular ejection fraction of 0.40 - 0.60 and a rise in ejection fraction on exercise of at least 0.05 except for the subject who had abnormal electrocardiograph (subject 17). In every case there was a rise in the heart rate to over 100 beats per minute on exercise. Resting cardiac output was 4.68 ± 1.21 (SD) l/min and there was the expected rise on exercise to 9.05 ± 2.76 l/min. The cardiac volumes also showed the expected normal responses to exercise with a rise in stroke volume (22 ± 14%, p < 0.001) and a fall in end systolic volume (-21 ± 16%, p < 0.001, fig 18). In no subject was the end systolic volume increased on exercise but 2 subjects failed to reduce their end systolic volume, probably implying that the work load was not sufficient stress to the myocardium.

Normal older subject group (age 35 - 54 years)
The individual data is shown in table 9. Six of this group of men had abnormal electrocardiographic exercise tests with ST segment depression of > 1 mm on exercise despite having no symptoms and a normal resting electrocardiogram. All subjects had a rise in heart rate to over 100 bpm on supine exercise during the radionuclide study. The resting and exercise ejection fraction were not significantly different from the younger subjects but it will be noticed that in 4 individuals there was no rise on exercise (fig 19).
Fig 18  Percentage change in end-systolic volume (ESV) with submaximal exercise related to age in a group of 59 normal subjects. The regression slope with 95% confidence limits of the slope are indicated.
Fig 19  Change in left ventricular ejection fraction (LVEF) with submaximal exercise related to age in a group of 59 normal subjects. The regression slope with 95% confidence limits of the slope are indicated.
Fig 20 Percentage change in end-diastolic volume (EDV) with submaximal exercise related to age in a group of 59 normal subjects. The regression slope with 95% confidence limits of the slope are indicated.
Fig 21 Change in heart rate (HR) with submaximal exercise related to age in a group of 59 normal subjects. The regression slope with 95% confidence of the slope are indicated.
Only 2 of these men had abnormal exercise tolerance tests. The fall in end systolic volume was not so consistent in the older subjects (mean change $-6 \pm 15\%$, NS, fig 18).

**Relationship between age and cardiac function**

For the total normal population ($n = 59$) there were interesting relationships between cardiac performance on exercise and age (figs 18-21). There was a weak correlation between age and change in ejection fraction on exercise ($r = -0.30$, $p < 0.05$), for the whole group. This correlation was still present if the subject with the very large increase in LVEF on exercise (0.27) was removed from the analysis.

The rise in cardiac output did not change with age (rise in CO [ml] = $115 - 0.5 \times \text{[age]}$, $r = -0.15$, NS). Heart rate rose less on exercise with age ($r = -0.48$, $p < 0.001$) and end diastolic volume on exercise rose with age ($r = 0.39$, $p < 0.01$). Interestingly the reduction in end systolic volume with exercise was not seen in the older group and it rose in some men such that the change in end-systolic volume was significantly correlated with age ($r = 0.42$, $p < 0.01$).

**COMPARISON WITH ANGINA GROUP**

The subjects were age-matched and selected from the same population sample. Interestingly, there was no difference in the ejection fraction at rest ($p = 0.83$), on exercise ($p = 0.50$) or the rise on exercise ($p = 0.12$) between the 43 normal individuals and the 36
matched angina subjects (table 10). There was a slight but significant difference with the heart rate rising more on exercise in the angina group ($p = 0.04$, see table 10). Stroke volume on exercise rose to a greater degree in the controls (+24 ± 1.9%) compared with the angina group (+13 ± 2.5%, $p = 0.0004$) but the increment in cardiac index on exercise was unchanged ($p = 0.18$).
DISCUSSION

Population selection

These normal subjects taken together span an age range of 25 - 54 years. They were all recruited from the community having not had any contact with the medical profession. In this way the population studied varies from previous hospital based studies (table 11), many of which have included patients with atypical chest pain (Manyari et al, 1983) or patients with revascularised coronary arteries following a presentation with angina (Iskandrian, 1987). Whilst many of these "para-normal" subjects have had coronary arteriography which showed them to be free of major coronary atheroma, it does not directly follow that their left ventricular function is representative of a normal population. Indeed Berger et al (1981) have shown that some patients with atypical chest pain and normal coronary arteries have very abnormal left ventricular function. Furthermore, such patients have been selected by a presentation with chest pain and may not be representative of the normal population. This might affect the data obtained.

To avoid these forms of bias, and to use a local population which might differ from the American patients previously studied we selected subjects who had not had cause to seek medical attention. Interestingly 6 of these asymptomatic subjects had abnormal electrocardiographic exercise tolerance tests. However, the interpretation of the significance of these abnormalities is not clear. In a population which has not been selected for
characteristics of ischaemic heart disease Bayes' theorem suggests that the sensitivity and more importantly specificity of such a test is low (Sheffield, 1984, see below).

The effect of exercise
For gated cardiac studies which take several minutes to collect, submaximal exercise is most appropriate. This type of exercise protocol also avoids the problem that older subjects have lower maximal exercise levels, which could make comparison between different age groups difficult. Hence a standard workload was used in these studies. A level of 75 watts supine exercise was chosen because the enhanced venous return in this position imposes a greater strain on the heart (Poliner et al, 1980) and this was the maximal workload which could be reasonably maintained.

In the younger group of men (age 25 - 34 years) the resting cardiac output was in the ranges quoted from other invasive and radionuclide studies and the expected rise on exercise was seen (Wade and Bishop, 1962, Iskandrian, 1987). The doubling of cardiac output (rest 4.68 l/min, exercise 9.05 l/min) was due to both a rise in heart rate and stroke volume, which contributed equally in a similar manner to previous studies. In all subjects the supine resting left ventricular ejection fraction was greater than 0.42 at rest and only the subject with an abnormal electrocardiograph showed a rise of less than 0.05 on submaximal supine exercise. The data is in agreement with the criteria for normal radionuclide cardiac function defined by Iskandrian (1987) from his review of the literature. He regarded a
normal result as a resting left ventricular ejection fraction of $> 0.45$ with a rise of $> 5\%$ on submaximal exercise. However, Poliner and co-workers (1980) noted that left ventricular ejection fraction was lower, and rose less on exercise in supine than erect young subjects, probably as a result of the increased venous return when supine. This explains why our data is towards the lower limit of normal values previously reported (Iskandrian, 1987). It also suggests that supine exercise places a greater demand on the heart at a given workload.

In the older men (age 35 - 54 years) the rise in ejection fraction on exercise was no longer consistent (fig 19). Port and colleagues (1980) have made a similar observation in a similar group of University Staff and people selected from an ageing study in North Carolina. In general their subjects were older than ours and the decrease in exercise left ventricular ejection fraction response was only apparent in people aged over 60 years.

It has been noted that the fall in end-systolic volume on exercise is the hallmark of a normal response (Vojacek et al, 1982; Iskandrian, 1987) regardless of age, level of exercise and position. Our data is in agreement with previous data but the same response was seen in the age-matched angina subjects selected from the community ($p = 0.81$) when compared with the older group of subjects suggesting that the ability of this measurement to exclude ischaemic heart disease is poor. The rise in stroke volume with exercise seen in our subjects was also in agreement with previous studies and this was
significantly greater in the healthy controls than the angina subjects ($p < 0.0005$). Removing the subjects with the abnormal exercise electrocardiograms from the analysis does not affect the interpretation of the data.

**THE EFFECT OF AGE**

The problems of differentiating between age-related changes in exercise cardiac function and those produced by occult ischaemic heart disease have been mentioned. Rodeheffer and his colleagues (1984) have suggested that exercise electrocardiography and exercise thallium scanning can reliably be used to exclude subjects with overt and occult ischaemic heart disease from normal population studies. However, this assumes that these investigations have a sensitivity and specificity of 100% which is not true (Sheffield, 1984). In other studies where older subjects (often up to 80 years old) have been studied, much of the decline in cardiac response to exercise could be related to occult coronary artery disease. The age range of our subjects is somewhat lower than that studied by other groups (table 11). Port and colleagues (1980) studied a group of 77 men and women to assess the effect of age on left ventricular function and nearly half of their subjects were over 60 years old and in the Baltimore longitudinal study of ageing (Rodeheffer et al, 1984) 61 subjects of whom 21 aged 60 - 79 years were studied. Much of the significance of the findings from these two studies can be attributed to the elderly patients having lower left ventricular ejection fraction and a smaller rise in ejection fraction on exercise. Our
study only considered people up to the age of 54 years so as to provide a population roughly matched to the study groups of patients with heart failure and hypertension studied below. It is interesting that even in these relatively young men there was a correlation between age and rise in ejection fraction on exercise of a similar degree \( r = 0.30 \) to that noted by Iskandrian \( r = 0.28 \) Port \( r = 0.70 \) and Rodeheffer \( r = 0.33 \). There was also a significant rise in end diastolic volume on exercise with age \( r = 0.39, p < 0.01 \), supporting the view that the Frank Starling mechanism (see chapter 1) is used to maintain cardiac output on exercise as age increases (Iskandrian, 1987). Cardiac output was not changed with age and rise in heart rate on exercise was significantly lower as age increased \( r = -0.48, p < 0.001 \). It is interesting that these changes were apparent in a younger population than previously studied. This implies that, at least in a Scottish population, age-related change in cardiac performance can be detected in people under the age of 55 years. Some of this could be due to occult ischaemic heart disease, and 6 men did have abnormal electrocardiographic exercise tests.

Exercise electrocardiography appears to have a sensitivity of about 80% and a specificity of 90% for ischaemic heart disease (Sheffield, 1984). If the normal population being studied has a low prevalence of ischaemic heart disease, for example 3% then the probability of a subject with positive exercise test having ischaemic heart disease is only 20% according to Bayes' theorem (Sheffield, 1984; Iskandrian, 1987). The predictive values of exercise thallium scanning are
unknown but unlikely to be superior. The most reliable way of reducing the incidence of occult ischaemic heart disease in a population so as to study the effect of age is to reduce the upper age limit of the study group.

The incidence of occult coronary artery disease increases rapidly in the fourth decade and is probably present in 50% of men by the end of the sixth decade (White et al, 1950). Exercise thallium scanning suggests it is occult in at least 50% of these (Gerstenblith et al, 1980). In Scotland, where the incidence of coronary artery disease is extremely high (Tunstall-Pedoe et al, 1986) the prevalence might be even greater assuming that occult disease is similarly high and hence the importance of studying a relatively large and young group of subjects. However, removing the data for the 6 men with abnormal exercise tests does not alter the interpretation of the data. Further in the subjects with angina derived from the same population there was no difference in left ventricular ejection fraction at rest or on exercise. This suggests that the technique is not a sensitive test for angina in the community. Previous studies have shown that the exercise ejection fraction is only reduced in patients with double or triple vessel coronary disease (Jones et al, 1981; De Pace et al, 1983). Unfortunately it is not reasonable to carry out coronary angiograms on normal subjects with the invasive techniques currently available. However, as even patients without evidence of cardiovascular disease, but with chest pain and normal coronary arteries, may have very abnormal left ventricular function (Berger et al, 1981) this investigation does not exclude abnormalities of
ventricular muscle function. It seems likely that coronary artery disease, perhaps of smaller vessels accounts for some of the age related changes in left ventricular function with exercise. However, we have evidence that there is probably also an ageing phenomenon independent of coronary artery disease.
CONCLUSIONS

In normal subjects derived from a Scottish community we have found that there is a very large variability in resting left ventricular ejection fraction and a variable response to exercise. With age the rise in ejection fraction on submaximal exercise tends to be less as does the rise in heart rate. This is associated with a rise in end diastolic volume with exercise and in older people the fall in end systolic volume is not consistent.

From our data normal in people under the age of 55 years can be defined as a resting left ventricular ejection fraction of > 0.44 with a rise on exercise in men under the age of 45 years. In men under the age of 40 years this rise is > 0.05. End-systolic volume is reduced on exercise and stroke volume and heart rate account about equally for the rise in cardiac output. The individual response is extremely variable.

In a group of subjects with angina pectoris who have not attended a physician there was no detectable abnormality in the rest and exercise ejection fraction or cardiac volumes. The individual responses were again very variable. Exercise radionuclide ventriculography will not consistently reliably detect cardiac dysfunction in men presenting with a history of angina pectoris and hence a normal exercise study does not exclude cardiovascular disease.
Previous definitions of normal cardiac radionuclide ventriculograms may not apply to our population, and particularly in older people. For studying patients with cardiovascular disease, it is important to realise the variability of the normal cardiac function and hence comparisons with other groups, or groups which are not age-matched, will be inappropriate.
CHAPTER 5
INTRODUCTION

The assessment of myocardial contractility in man is difficult (Hamer, 1978) but central to study of the cardiovascular system. Braunwald (1984) has defined a change in inotropic or contractile state as "an alteration in cardiac performance that is independent of changes resulting from variations in preload or afterload". It is well established that myocardial contractility can be modulated through the beta-adrenergic system and there are many drugs available which act on myocardial beta-receptors allowing study of the effects of altering contractility (Frishman, 1979). Inotropic agents are accepted agents in the management of acute heart failure complicating myocardial infarction and beta-blockade is used in the management of hypertension.

The purpose of the studies described here was to investigate the changes in the circulation produced by drugs affecting contractility through the adrenergic system. The mechanism of action of beta-adrenergic blockade in hypertension has not been established (see discussion in chapter 1) and it has been suggested that propranolol might correct the abnormalities of blood volume distribution seen in hypertensive patients (see chapter 1). We therefore studied the effects of the beta-blocker atenolol on the central blood volume and peripheral vascular resistance in patients with essential hypertension. To determine the effects of pirbuterol, which was
thought to have an inotropic action in addition to beta_2-dilator properties, we studied right ventricular function in a group of patients with stable cor pulmonale, acutely with the pure vasodilator sodium nitroprusside and the sympathomimetic agent pirbuterol.
THE CARDIOVASCULAR EFFECTS OF ATENOLOL IN ESSENTIAL HYPERTENSION

The aetiology of essential hypertension is unknown (see chapter 1) but the condition is characterised by elevated peripheral vascular resistance (Lund Johansen, 1980). There is also evidence that central blood volume is increased at an early stage in the development of essential hypertension by a shift of blood from the peripheral to the central compartment (Ulrych et al, 1969; Safar et al, 1974; Mackay et al, 1984) and this may be one of the fundamental circulatory abnormalities in the development of sustained high blood pressure (de Wardener and McGregor, 1982). The effects of antihypertensive drug therapy on this fluid shift are unknown but Kraus and his colleagues (1972) have suggested that propranolol, rather surprisingly, prevents the rise in central blood volume which is produced by saline infusion in patients with essential hypertension. They thought that this was due to a peripheral vasodilation. The antihypertensive effects of beta-adrenergic blocker therapy are not well understood (see chapter 1) but these effects on blood volume distribution might be important. I have therefore examined the effects of atenolol on central haemodynamics and peripheral vascular resistance in patients with previously untreated WHO stage 1 essential hypertension.
Patients

Thirteen men (aged 39 - 61) years were recruited from the Hypertension Clinic. They were selected because they had WHO stage 1 essential hypertension with no evidence of "end organ" damage (World Health Organisation, 1959) and had not previously been treated with any antihypertensive medication. None had taken any cardiovascular drug for a period of at least 3 months. They had no clinical or electrocardiographic evidence of ischaemic heart disease and did not receive treatment for any chronic medical condition. Blood pressure had been recorded as > 145/105 mmHg (diastolic phase V) on three occasions over a period of at least 6 weeks. All gave informed consent to the study and approval was obtained as described above.

Methods

The patients attended the laboratory for an explanation of the study and to familiarise them with the equipment on the day of their final blood pressure measurement. They returned to the laboratory for a second visit in the morning after a light breakfast. After lying for 15 minutes on the examination couch during which time a Venflon cannula was sited in the right antecubital fossa for measurement of cardiac output and another one in the left cubital fossa for blood sampling as described previously, the study was commenced. Blood pressure was recorded using an automatic blood pressure recorder (Critikon Model 1160) using the phase V diastolic recording. With the radionuclide methodology described above (chapter 3) cardiac output, pulmonary transit time, left ventricular ejection fraction
and heart rate were determined after injection of a bolus of 700 mBq of $^{99m}$Tc electrolytically labelled to human serum albumin. Immediately after making the first pass bolus study, a gated equilibrium study was carried out so that the left ventricular outline could be more precisely defined. Mean pulmonary transit time was measured using the isotope dilution curves of passage of the isotope from the pulmonary artery to the left ventricle with a correction for the left atrium (fig 22). The validation of this method has been described previously (Hannan et al, 1981; see chapter 3). Pulmonary blood volume was then calculated.

Pulmonary blood volume

\[
(1) \quad \text{cardiac output (1 min}^{-1}) \times \text{mean pulmonary transit time (sec)} = \frac{\text{mean arterial pressure (mmHg)}}{60}
\]

Mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure and the peripheral vascular resistance was calculated as the mean arterial pressure divided by the cardiac output:

Peripheral vascular resistance

\[
(Dyn.s.cm^{-5} m^{-2}) \quad \text{mean arterial pressure (mmHg)} \times 0.7994 = \frac{\text{cardiac output (1 min}^{-1})}{60}
\]
Fig 22  Isotope counts detected over pulmonary artery (a) and left ventricle (b) after the injection of a bolus of Tc$^{99m}$ into the right forearm. The mean pulmonary transit time can be calculated as $\text{MTT}_1 - \text{MTT}_p$. The cardiac output can be derived from the area under the isotope dilution curve of the left ventricle (A) and the right end equilibrium (H).
Total blood volume was calculated from the dilution of the labelled albumin in the blood pool. We have previously shown that this technique agrees with standard $^{125}\text{I}$iodine determinations (Millar et al, 1979). Plasma samples were taken for urea, electrolytes, creatinine, glucose, full blood count, and plasma renin activity.

After the initial study, patients were commenced on atenolol 100 mg daily and the blood pressure response monitored at 3 weekly intervals. Repeat radionuclide studies were carried out after 16 weeks of therapy if blood pressure control had been satisfactory (supine blood pressure < 150/95 mmHg). Those patients who did not have adequate control of their blood pressure on this therapy were excluded from the study. At the time of repeat study plasma samples were taken for atenolol analysis. Statistical analysis was carried out by Student's $t$ test for paired data and values of $p > 0.05$ were considered not significant.

RESULTS

Eleven patients (age 39 - 61 years) completed the study; 2 of the original 13 were excluded because of inadequate control of blood pressure and the full results were not available in two further studies for technical reasons. The characteristics of the 11 patients completing the study are shown in table 12. The measured data and the data derived from this is summarised in table 13.
Initial haemodynamics

Blood pressure at entry was 185/113 ± 23/8 (SD) mmHg, pulse rate was 74 ± 20 bpm. Cardiac index was 4.0 ± 0.65 1 min⁻¹m⁻² (body surface area 1.93 ± 0.11 m²) giving a stroke volume index of 55 ± 8.7 ml m⁻². LVEF was 0.53 ± 0.076 at rest and was not significantly altered by exercise (0.53 ± 0.060). The mean pulmonary transit time was 7.5 ± 1.15 sec and from this the pulmonary blood volume index was calculated as 502 ± 96 ml m⁻². The peripheral vascular resistance index was elevated at 2797 ± 509 dyn.s.cm⁻⁵.m⁻². There were no significant abnormalities in full blood count, urea or electrolytes, or liver function tests. The plasma renin activity at entry was 1.11 ± 1.13 ng.ml⁻¹.h⁻¹.

Haemodynamics after atenolol therapy

Plasma assay for atenolol confirmed compliance in all subjects. Body weight and total blood volume were not significantly changed. Because of the patient selection, the blood pressure was reduced to 132/86 ± 13/6 mmHg. Heart rate fell to 62 ± 11.5 bpm (p < 0.01) and the reduced heart rate on exercise confirmed beta-blockade (table 13). Cardiac index was lower (3.4 ± 0.61 1⁻¹min⁻¹.m⁻²) due to the fall in heart rate. Stroke volume index was not changed (55 ± 8.8 ml m⁻²), LVEF was 0.55 ± 0.070 at rest and again was unchanged by exercise. The mean pulmonary transit time was 8.4 ± 0.62 seconds and despite the change in cardiac index, the pulmonary blood volume index was not significantly changed. Peripheral vascular resistance was not altered significantly (2447 ± 591 dyn.s.cm⁻⁵.m⁻², NS).
DISCUSSION

Atenolol was chosen for the study because it has no intrinsic sympathomimetic activity, is highly selective for $B_1$ adrenoceptors and has a very flat dose response curve (McDevitt, 1979) such that the effective dose could be easily determined. In this group of patients who were selected because their blood pressure responded to therapy with atenolol, the other cardiovascular changes are of interest. Cardiac output was significantly reduced such that peripheral vascular resistance was not altered. This finding is in agreement with that of Lund Johansen (1976). The reduction in cardiac output was achieved entirely through a reduction in heart rate. This is perhaps not surprising as venous filling of the heart may be improved by the slower heart rate and tend to prevent a reduction in stroke volume with falling cardiac output. The stroke volume is known to be subnormal in essential hypertension, given the cardiac output (Lund Johansen, 1967) such that the maintenance of stroke volume may reflect more favourable cardiac haemodynamics.

The high peripheral vascular resistance deserves further comment. The lack of any reduction change is further evidence that atenolol does not have vasodilator effects on the arterial system. Raised peripheral vascular resistance is the consistent finding in essential hypertension (Safar et al, 1974; Lund Johansen, 1983; Birkenhager and de Leeuw, 1984) and has been confirmed in our laboratory (Mackay et al, 1984). Therefore, from a pathophysiological point of view atenolol may have less favourable haemodynamic effects than drugs.
with vasodilator properties. Man in t'Veld and Schalekamp (1983) have reviewed the haemodynamic consequences of beta-adrenergic blockade in essential hypertension. They observed that the reduction in peripheral vascular resistance is related to the degree of intrinsic sympathomimetic activity and our data is in agreement with their observations (see fig 23). It follows that the findings of this study of atenolol cannot be extrapolated to other beta-blocking agents with other properties. Peripheral vascular resistance can only be calculated from cardiac output (and arterial pressure) so the value of this correlation has been questioned (Birkenhager and de Leeuw, 1984). Nevertheless it seems reasonable to suppose that there might be benefits from reducing the elevated peripheral vascular resistance as well as reducing the cardiac output in a state where the cardiac output is already subnormal, as discussed in chapter 1.

From this study it is impossible to assess whether there has been a subtle change in inotropic state with atenolol but this is probably so. Inotropic state in intact man depends in part upon the stimulation of adrenergic receptors, and in the heart most of these are of beta1-type (Lands et al, 1967; Watonabe, 1983). At rest, in hypertensive subjects, there will be little activation of the sympathetic nervous system and the circulating catecholamine levels will be low, such that atenolol is unlikely to have much negative inotropic effect. However, the adrenergic system is active because a negative chromotropic effect is observed with atenolol therapy as shown in our study.
The change in systemic vascular resistance and cardiac output with chronic beta-blocker therapy in patients with essential hypertension. (The present study of atenolol is indicated).
On exercise the catecholamine stimulation of the beta<sub>1</sub> receptor will be greater and the effects of atenolol more apparent. Blockade of the compensatory catecholamine response to a negative inotropic effect on the heart, for example, induced by drugs is unlikely to be detected unless this is prevented by beta-adrenoceptor blockade (Aoki et al, 1978; see chapter 6).

The second problem is the detection of intrinsic change in the inotropic state of the myocardium in the presence of a reduced afterload (blood pressure), as produced by atenolol. The inotropic state is also dependent upon the Frank-Starling mechanism and is discussed more fully in the following section in relation to pirbuterol therapy. The reduction in heart rate and systolic blood pressure by atenolol means that the rate-pressure product will be reduced, implying that the myocardial oxygen consumption will be lower (Blackburn et al, 1970). In the absence of stress it would therefore be extremely difficult to detect any change in inotropic state.

The central or pulmonary blood volume is high in essential hypertension (Ulrych et al, 1969; Safar et al, 1974) and this might lead to the elevation of blood pressure as discussed in chapter 1. Because the way in which beta-blockers control hypertension is not known (see chapter 1), and propranolol has been shown to produce a shift of blood from the central to the peripheral venous system during plasma volume expansion (Krauss et al, 1972) it was
interesting to examine the effects of atenolol on blood volume distribution. The pulmonary blood volume and the ratio of pulmonary to total blood volume were not significantly changed by atenolol therapy despite control of blood pressure. Unfortunately the determination of pulmonary blood volume is dependent upon the measurement of cardiac output but the fall in cardiac output with atenolol would tend to reduce the pulmonary blood volume. Such a reduction was not seen in this study and thus it seems unlikely that atenolol therapy corrects this haemodynamic abnormality. Indeed in our patients atenolol reduced cardiac output without changing peripheral vascular resistance suggesting that atenolol produces its beneficial effect in hypertension by a reduction in cardiac output.

It is interesting, and rather disappointing, that widespread use of beta-adrenergic blocking drugs in the treatment of hypertension has failed to produce any beneficial effect in relation to the increased risk of myocardial infarction whilst producing benefit in stroke and renal disease (MRC 1985; Wilhelmsen et al, 1987). It is clear that the reduction in stroke and renal failure is related to the reduction in blood pressure but it is possible that a reduction in the incidence in cardiac disease in hypertensive subjects might only be achieved by reducing the resistance against which the heart is pumping, that is the peripheral vascular resistance. From this study and others (Lund Johansen, 1976) it is apparent that atenolol will not do this and there is no data about the effect of vasodilator therapy, which would be likely to lower the peripheral vascular resistance, on cardiovascular morbidity or mortality in relation to
hypertension. Before such a trial were mounted, it would be important to show that any proposed drug had beneficial haemodynamic effects as well as producing a sustained fall in peripheral vascular resistance. The methods used in this study would probably be suitable for such studies.
THE EFFECTS OF PIRBUTEROL AND SODIUM NITROPRUSSIDE ON RIGHT HEART FUNCTION IN COR PULMONALE

Pirbuterol is a beta-sympathomimetic drug structurally similar to salbutamol. Animal studies have shown that its principal cardiovascular effect is vasodilation (Moore et al, 1978) but similar animal experiments have shown it to have a positive inotropic action (Gold and Horowitz, 1981; Constantine, 1978). In contrast, sodium nitroprusside is a pure vasodilator. Because of the theoretical attraction of using a combined pulmonary vasodilator and inotrope for the treatment of right heart failure in cor pulmonale (see chapter 1), we investigated the acute haemodynamic effects of pirbuterol in such a group of patients and contrasted it with the vasodilator effects of sodium nitroprusside in the same group of patients.

Patients

Six men and 6 women (aged 42 - 72 years) with chronic bronchitis and emphysema (FEV$_1$ 0.65 ± 0.20, (SD); FVC 1.75 ± 0.59 l) were studied (table 14). All of the patients were significantly hypoxic when breathing air (PaO$_2$ 7.3 ± 0.28 kPa) and most had a degree of hypercapnia (PaCO$_2$ 6.4 ± 0.70 kPa). All were stable at the time of study but had in the past developed cor pulmonale with ankle oedema (World Health Organisation, 1963). Body weight and FEV$_1$ had been stable for 3 weeks prior to study and at the time of study none had acute respiratory infection or peripheral oedema. No patient had any drug therapy on the day of the study. All had been receiving beta$_2$ agonists and ipratropium bromide inhalers and oral diuretics.
One patient was taking digoxin. All patients consented to the study and permission to conduct the study was obtained.

Methods

The patients were studied at rest after the insertion of a Swann Ganz type pulmonary artery catheter (Edwards Laboratories) and a short period for acclimatisation. Measurements were taken for control observations, during an intravenous infusion of sodium nitroprusside, which was titrated to a dosage which would produce a fall in systolic arterial blood pressure of approximately 10 mmHg (1-5 ug/kg body weight) and then at intervals of 30 minutes for 120 minutes after an oral dose of pirbuterol tablets. Only 10 of the 12 patients received the intravenous sodium nitroprusside infusion and only when the haemodynamic variables had returned to normal after ceasing the infusion was the pirbuterol given. In the other two patients, sodium nitroprusside was not given to examine the possibility that this drug might alter the data subsequently recorded for pirbuterol. The effective dose of pirbuterol was unknown so 6 patients received 15 mg and a further 6 patients 22.5 mg. Plasma samples for assay of pirbuterol were taken at 60 and 120 minutes after dosing. Heart rate and ear oxygen saturation, using a Hewlett Packard (47201A) ear oximeter, were measured continuously. Arterial blood pressure was measured by conventional sphygmomanometry using a random zero sphygmomanometer phase V diastolic reading. Right atrial, right ventricular and pulmonary artery pressures were measured with the Swann Ganz flow directed triple lumen catheter. Measurements were averaged over five respiratory cycles and all intracardiac pressures
were referenced to the right atrium taken as 5 cm below the sternal angle. Cardiac output was measured in triplicate by cold saline thermodilution.

Left and right ventricular ejection fractions were measured after the intravenous injection of 750 mBq technetium$^{99m}$ labelled to human serum albumin as described previously except that in order to separate the ventricles on the scans in these patients it was found necessary to use the 20° left anterior oblique position with 10° caudal tilt for the gamma camera.

**Statistical analysis**

Differences between means were compared with a paired t test or with analysis of variance where repeated measurements were made.

**RESULTS**

The mean data for the groups given the two different doses of pirbuterol were combined because although the mean plasma levels achieved were a little higher with the larger oral dose there was considerable individual variation (table 15), the results were not significantly different (fig 24). The individual patient characteristics with the mean data for the group are shown in tables 14 and 16.

The maximum effects of pirbuterol were noted 90 minutes after oral dosing in general (fig 24) and therefore this data was used for
Fig 24  The mean pulmonary artery pressure and cardiac output in 12 patients with COLD following oral pirbuterol. The patients given 15 mg pirbuterol are shown as open circles (○) and those given 22.5 mg pirbuterol as closed circles (●).
analysis. Similar but less pronounced changes were seen at 60 and 120 minutes.

**Sodium nitroprusside**

The heart rate increased from $87 \pm 13$ (SD) to $96 \pm 16$ bpm and mean blood pressure fell from $93 \pm 13$ to $72 \pm 5$ mmHg ($p < 0.01$). This was not associated with a significant change in cardiac index such that there was a fall in systemic (peripheral) vascular resistance from $1819 \pm 588$ to $1271 \pm 272$ dyn.s.cm$^{-5}.m^{-2}$ ($p < 0.05$). There was a fall in pulmonary artery pressure, from $30 \pm 6$ to $22 \pm 6$ mmHg ($p < 0.01$) so that the total pulmonary vascular resistance fell significantly ($p < 0.001$). There was a rise in both left ($p < 0.05$) and right ($p < 0.05$) ventricular ejection fractions assessed by radionuclide ventriculography. Stroke volume index was slightly reduced ($31 \pm 8$ to $28 \pm 7$ ml.m$^{-2}$, $p < 0.001$) and these changes were not associated with any change in ear oxygen saturation. The calculated ratio of right ventricular systolic pressure to right ventricular end-systolic volume did not change (fig 25). Using systolic blood pressure as an approximation of left ventricular end-systolic pressure the calculation ratio for left ventricular end-systolic pressure to end-systolic volume was also unchanged (fig 26).

**Pirbuterol**

In contrast to the results with sodium nitroprusside, pirbuterol produced a rise in heart rate of $10 \pm 10$ bpm ($p < 0.01$) but no change in systemic blood pressure. Cardiac index was significantly increased from $2.62 \pm 0.58$ to $3.15 \pm 0.62$ ml.m$^{-2}$ ($p < 0.001$) such that
The relationship between RV end-systolic pressure and RV end-systolic volume index in 10 patients with COLD and the changes produced by sodium nitroprusside and pirbuterol.
The relationship between systolic blood pressure (as an approximation of LV end-systolic pressure) and LV end-systolic volume index in 10 patients with COLD and the effects of sodium nitroprusside and pirbuterol.
systemic vascular resistance was reduced \( (p < 0.001) \). Pulmonary arterial pressure was reduced slightly with the mean falling from \( 30 \pm 5 \) to \( 27 \pm 5 \) mmHg \( (p < 0.05) \) such that the total pulmonary vascular resistance was significantly reduced \( (p < 0.001) \). There was no significant rise in left ventricular ejection fraction but the right ventricular ejection fraction was significantly increased by pirbuterol \( (p < 0.01) \). Pirbuterol in contrast to sodium nitroprusside produced a small increase in stroke volume index of \( 3 \pm 8 \) ml \( (p < 0.05) \). With pirbuterol there was a tendency for the ear oxygen saturation to fall and arterial \( PO_2 \) did fall from \( 7.3 \pm 0.8 \) to \( 6.6 \pm 0.9 \) kPa \( (p < 0.05) \), although because of the increased cardiac output the tissue oxygen delivery was probably little altered. There was no significant change in arterial carbon dioxide concentration. There was no correlation between the plasma concentrations of pirbuterol and the changes in pulmonary artery pressure. There was a tendency for the ratio of left and right ventricular end-systolic pressure to volume ratios to increase (figs 25 and 26).
The primary aim of this study was to examine whether any pulmonary vasodilator or inotropic effects of pirbuterol on the right ventricle and pulmonary circulation could be demonstrated in patients with chronic bronchitis and emphysema. The mechanism of the haemodynamic effect of pirbuterol in clinical practice are debated (Dawson et al, 1981; Sharma et al, 1981; Nelson et al, 1982) and the difficulty in differentiating the vasodilator and inotropic properties of this beta-agonist relate to the changes in ejection phase indices with reduction of afterload and the changes produced by secondary activation of the sympathetic nervous system. By simultaneous assessment of changes in right ventricular pressure and volume, we proposed to observe the pressure-volume relationships of the right ventricle at end-systole. Sagawa et al (1977) have shown for the left ventricle that the relationships between end-systolic pressure and volume are independent of the loading of the ventricle but sensitive to inotropic change in the dog and this has been confirmed in man (Braunwald, 1981; Millar et al, 1981; fig 27). The same situation should pertain to the right ventricle, particularly in the presence of raised pulmonary artery pressure. It was proposed to compare the effects of pirbuterol with the vasodilator sodium nitroprusside, which has no inotropic properties. From the data in our patients, sodium nitroprusside can be seen to have reduced right ventricular pressure and volume. This drug is a pure vasodilator and hence the relationship is the same at different end-systolic volumes, regressing towards zero (fig 25). The dose was titrated
Fig 27  Ventricular pressure-volume relationships.

a. Two different levels of afterload with preload and contractility unaltered (ABCD and AEFG).

b. Effect of increasing contractile state.
such that there was a modest fall in systemic blood pressure to avoid
a significant sympathetic response. Pirbuterol was seen to produce
a smaller reduction in end-systolic pressure than volume, relative to
sodium nitroprusside. This suggests a small, but detectable
positive inotropic action (fig 25). A similar effect was seen in
the left ventricle (fig 26). However, most of the beneficial
effects must be due to vasodilation. The pulmonary vascular
resistance fell considerably despite only a small fall in pulmonary
artery pressure because of the rise in cardiac output. With sodium
nitroprusside, there was a greater fall in pulmonary artery pressure
but no significant change in cardiac output.

This weak positive inotropic action of pirbuterol may be beneficial
because pure pulmonary vasodilation may induce increased ventilation
perfusion mismatching (see chapter 1) from the reduction in pulmonary
arterial pressure. A positive inotropic action, might be beneficial
by maintaining cardiac output and thereby increasing tissue oxygen
delivery. Bergofsky (1983) has suggested that the prognosis in
patients with chronic bronchitis and emphysema is related to cardiac
output and maintenance of tissue oxygen delivery.

The right heart clearly works in conjunction with the left heart such
that left heart function and the systemic circulation might determine
the function of the right heart. In cor pulmonale the limitation
would appear to be in the pulmonary circulation such that it is
reasonable to believe the study of drug action on the right ventricle
and pulmonary circulation in these circumstances is not just
reflecting changes in the systemic circulation which pirbuterol is known to have (Dawson et al, 1981; Nelson et al, 1982).

Both sodium nitroprusside and pirbuterol produced a fall in peripheral (systemic) vascular resistance but in the case of sodium nitroprusside, this was caused by a fall in arterial blood pressure whilst with pirbuterol the fall was produced largely by a rise in cardiac output. The lack of effect of pirbuterol on systemic blood pressure implies that there was some specificity to the pulmonary vasodilator effect not seen with sodium nitroprusside. Further support for the specific pulmonary vasodilator effects of pirbuterol comes from the fact that pirbuterol produced a greater percentage fall in pulmonary than systemic vascular resistance whereas sodium nitroprusside showed no specificity and produced a similar percentage reduction in both systemic and pulmonary vascular resistance.

These haemodynamic effects of pirbuterol in patients with cor pulmonale have now been confirmed independently by Peacock and colleagues (1983).

In summary pirbuterol when given to patients with chronic bronchitis and emphysema reduces the elevated pulmonary artery pressure and the pulmonary vascular resistance largely due to a vasodilator effect on the pulmonary circulation, for which it shows some specificity but using the technique described a weak inotropic action can also be detected.
CONCLUSIONS

Studies using drugs to modulate the adrenergic system in intact man have been carried out. The cardioselective beta-blocker atenolol has been shown to reduce cardiac output and blood pressure without any reduction in peripheral vascular resistance or change in the distribution of blood volume between the central and peripheral compartments and it therefore seems that its antihypertensive action is caused by the negative chromotropic effect reducing cardiac output.

Investigation of the acute effects of the new sympathomimetic compound pirbuterol in patients with cor pulmonale showed that by comparing the effects with a pure vasodilator, sodium nitroprusside, it was possible to analyse the inotropic and vasodilator properties independently. The main effect of pirbuterol was a selective pulmonary vasodilator action. In addition a small positive inotropic action was noted and this acute study suggested that pirbuterol might be of benefit to patients with cor pulmonale and pulmonary hypertension.

These two studies in heart failure and hypertension show that modulation of the heart and circulation through adrenergic receptors is possible and the effects of such intervention can be measured. However, clinical benefit can only be assessed by an appropriate clinical trial. It was also suggested that for the management of hypertension, vasodilator therapy might prove more beneficial than
beta-blockade.
CHAPTER 6
INTRODUCTION

Therapy with vasodilators seems attractive in hypertension (Koch-Weser, 1974) and cardiac failure (Braunwald, 1981) as discussed in chapter 1. In both of these conditions the reduction in arterial tone would reduce the load on the heart but the circulatory effects of reducing arterial pressure are not clear. In heart failure the benefits of reducing cardiac filling pressure are more obvious (see chapter 1). It is established that the primary vascular abnormality in hypertension seems to be elevated peripheral or systemic vascular resistance (Lund Johansen, 1980) which develops as a result of increased arterial tone (Folkow et al, 1973). This may be an effect of altered vascular regulation and vasodilator therapy might offer a way of reversing the abnormalities in blood pressure, and vascular resistance seen in hypertension.

For hypertensive subjects the benefits may be confined to arteriolar vasodilation and this type of vasodilation seems a logical progression from current medical therapy. Until the aetiology of hypertension is understood, it will be difficult to provide specific antihypertensive treatment. However, vascular abnormalities in hypertension are well characterised (see chapter 1) and it would be more rational to correct these than merely lower the arterial blood pressure.
Unfortunately vasodilator therapy often leads to tachyphylaxis due to reflex induced tachycardia and fluid retention and necessitates the concurrent use of beta-adrenergic blocking therapy and sometimes diuretics. Slow calcium channel blocking agents (calcium antagonists) may not be so prone to these problems (Sorkin et al, 1985) but the currently available drugs may have adverse effects on myocardial contractility (Joshi et al, 1981; Serruys et al, 1981). Combination with beta-blockade might be beneficial but might compound the problem of reduced inotropism.

Studies were therefore designed to answer the following questions:

1. Does nifedipine significantly affect inotropic state or produce postural hypotension, particularly when combined with a beta-adrenergic blocking agent?

2. Does the new calcium antagonist felodipine affect venous tone and does it offer any advantage over the currently available agents?

3. Does a calcium antagonist offer therapeutic benefit in severe hypertension where conventional therapy is inadequate?

I therefore decided to use the radionuclide methods described above to investigate the effects of calcium antagonist vasodilators on the cardiovascular system following the promising results and went on to a trial of vasodilator therapy in severe hypertension.

All the studies described had the approval of the hospital ethical
committee and were carried out using patients recruited from the general Hypertension Clinic at the Royal Infirmary, Edinburgh. In addition, all studies of felodipine were approved by the Committee on Safety of Medicines.
THE ACUTE HEMODYNAMIC RESPONSE TO EXERCISE IN HYPERTENSIVE SUBJECTS GIVEN AFTERLOAD REDUCTION WITH NIFEDIPINE

Altered vascular smooth muscle tone is considered the major contributing factor to the development of high blood pressure as outlined above (see chapter 1). Therapy with vasodilators seems a logical approach (Koch-Weser, 1974). Exercise poses increased stress on the cardiovascular system of patients with hypertension and it is not known how this may be modified by vasodilators and calcium antagonists in particular. We therefore decided to assess the effects of nifedipine on cardiovascular function at rest and during upright exercise in hypertensive patients who had not previously been treated or were being treated with atenolol.

Patients
Sixteen male patients (aged 25 - 54 years) were recruited for the study. Ten had received no therapy and 6 were selected because they were receiving atenolol 100 mg daily for hypertension. All had WHO stage 1 hypertension (World Health Organisation, 1959) and none had clinical or electrocardiographic evidence of ischaemic heart disease. None had taken any other cardiovascular drug previously or was suffering from any chronic illness.

Methods
Studies were carried out with the patients sitting upright on a standard bicycle ergometer (Siemens). Heart rate was monitored continuously and blood pressure recorded by conventional
sphygmomanometry (using a mercury sphygmomanometer). This method was chosen because of difficulty producing reliable data with an automatic recorder during exercise (diastolic phase 5). Standard gated radionuclide ventriculography was carried out as described above with plasma sampling for blood clearance. Cardiac volumes and peripheral vascular resistance were calculated as described previously. The ejection phase indices, peak rate of change of left ventricular volume \((dV/dt)\) and mean left ventricular ejection time (corrected for heart rate, MET/LVET) were also calculated from the radionuclide ventriculogram.

**Study period**

Resting measurements were made after the patient had been seated on the bicycle for 15 minutes. After the resting ventriculogram had been taken, exercise ventriculogram was carried out with the patient exercising in 50 watts on the bicycle ergometer. The control observations were then carried out when the heart rate was stable. Following these measurements the patient was given 10 mg of sublingual nifedipine as a capsule (Adalat, Bayer) to chew. Blood pressure and heart rate were monitored at 2 minute intervals until the heart rate and blood pressure had achieved a new steady state. This was approximately 35 minutes after ingestion of nifedipine and ranged from 25 - 45 minutes. During this period the patients were re-seated on the bicycle ergometer for resting observations and then finally exercise was repeated at the same workload during which repeat ventriculography was carried out.
Statistical methods

Analysis was by the appropriate Student's t test and values of $p > 0.05$ were considered not significant. Where multiple measurements were made analysis of variance was used.

RESULTS

No patient complained of adverse effects after receiving nifedipine although in 4 patients there was noticable facial flushing. The results (mean $\pm$ SEM) from previously untreated patients (group 1) and from those previously treated with atenolol (group 2) are summarised in table 17. The two groups of patients had similar blood pressures at rest (fig 28).

EFFECT OF NIFEDIPINE ON HAEMODYNAMICS IN UNTREATED PATIENTS

Rest - Group 1

Systolic blood pressure was not significantly lower than in the control period ($-6 \pm 3$ mmHg) but diastolic pressure was reduced from $103 \pm 2.7$ to $89 \pm 3.3$ mmHg ($p < 0.005$) (fig 28). Heart rate rose from $85.8 \pm 4.7$ to $101 \pm 6$ bpm ($p < 0.01$). There was increase in the relative cardiac output of $44 \pm 9\%$ ($p < 0.005$). Stroke volume increased by $22 \pm 8\%$ ($p < 0.01$) (fig 29). The calculated peripheral vascular resistance was reduced by $34 \pm 15\%$ ($p < 0.005$). Left ventricular ejection fraction increased from a control value of $0.61 \pm 0.03$ to $0.68 \pm 0.03$ ($p < 0.005$) (fig 30). Calculated end-systolic left ventricular volume fell slightly but not significantly ($91.5 \pm$...
Fig 28  Systolic, diastolic blood pressures and heart rate, at rest and during upright bicycle exercise before and after nifedipine (x _ SEM) in untreated hypertensive patients and patients taking atenolol.
Fig 29  Percentage change in end-diastolic volume (EDV), stroke volume (SV) and cardiac output (CO) from baseline with exercise and after nifedipine therapy (x ± SEM) in untreated hypertensive patients and in a group taking atenolol.
Fig 30 Change in left ventricular ejection fraction (EF), the rate of change of left ventricular volume (dV/dt) and the ratio of mean left ventricular ejection time to total left ventricular ejection time (MET/LVET, which describes the change in shape of the systolic phase of the LV volume curve and is reduced by increased contractility).
7.4% from 100%). Peak rate of change of left ventricular volume (dV/dt) was increased (p < 0.005) and the ratio of mean ejection time to left ventricular ejection time was shortened (p < 0.01), both compatible with reduced left ventricular afterload.

**Exercise - group 1**

In all patients heart rate increased during exercise, the mean rising from 86 ± 5 to 107 ± 12 bpm (p < 0.001) with exercise (fig 28). Systolic blood pressure increased in all patients with a mean rise of 25 ± 3 mmHg (p < 0.001). In 2 of the 11 patients diastolic blood pressure fell during exercise but the mean change was an increase of 7 ± 3 mmHg (p < 0.02). There was a 79 ± 13% increase in cardiac output during exercise (p < 0.001) and a 42 ± 11% increase in stroke volume (p < 0.005). In 6 of the 10 patients there was an increase in ejection fraction on exercise. In one patient the change during exercise could not be measured satisfactorily for technical reasons and in 3 other patients there was a fall in ejection fraction on exercise. These 3 patients could not be distinguished on the basis of age, systolic or diastolic blood pressure but their resting ejection fractions were high (0.65, 0.63, 0.84).

**Effect of nifedipine on exercise - group 1**

Exercising at the same workload after nifedipine caused an increase in heart rate of 23 ± 3 bpm (p < 0.001) but this was not significantly different from the exercise pre-treatment period (fig 28). Similarly the mean increase in systolic and diastolic blood pressure was not significantly different from the pre-treatment
period (fig 28). During exercise in addition to the 3 patients who already showed no increase in LVEF on exercise, there was one further patient who had a fall in LVEF. The group had no change in mean left ventricular ejection fraction on exercise after nifedipine (fig 30).

**THE EFFECT OF NIFEDIPINE ON RESTING HEMODYNAMICS IN BETA-BLOCKED PATIENTS**

**Rest - group 2**
There was a significant fall in systolic and diastolic blood pressure ($p < 0.01$) but the increase in heart rate was less marked ($7 \pm 2.7$ bpm, $p < 0.05$) (fig 28). There was no increase in stroke volume, a smaller increase in cardiac output ($+11.2 \pm 9\%$) than in those not treated with atenolol and indices ventricular emptying were not significantly altered (fig 30).

**Exercise - group 2**
The blood pressure and heart rate response to exercise was very similar to the response in patients not pre-treated with atenolol (figs 28-30). Similarly, there was no difference in the response to exercise of stroke volume or cardiac output. For this group the ejection phase indices (fig 30) were not significantly different from the control period.

**The effect of nifedipine on exercise - group 2**
Given the different starting levels, the increases in blood pressure
and heart rate during exercise were similar (fig 28). However, the peak levels achieved were different, the systolic blood pressure being 20 mmHg lower on those pre-treated with atenolol and the heart rate being 30 bpm less at the same exercise level. In this group with the lower resting ejection fraction following nifedipine, there was an increase in ejection fraction during exercise (0.58 ± 0.02 after nifedipine, 0.62 ± 0.02 after exercise, p < 0.05).

End-systolic pressure volume relationships were derived by plotting the systolic blood pressure as an approximation to left ventricular end systolic pressure and the relative change of end-systolic volume on exercise before and after nifedipine in the two groups (fig 31). The combination of beta-blockers and nifedipine produced a downward movement with increase in end-systolic volume with decreasing systolic blood pressure. This implies a negative inotropic effect.
Fig 3.1 Relationship between systolic blood pressure (SBP) as an approximation of left ventricular end-systolic pressure and percentage change in end-systolic volume (ESV) in previously untreated patients and beta-blocked hypertensive patients when given nifedipine. The beta-blocked group are below and to the right of the untreated group indicating a negative inotropic effect.
DISCUSSION

The effects of nifedipine with and without beta-blockade on response to exercise in patients with moderate essential hypertension have been assessed. Two groups of patients with similar levels of blood pressure have been studied to facilitate the comparison. For this reason a crossover design was not possible. In both groups nifedipine produced a significant fall in blood pressure accompanied by a marked decrease in peripheral vascular resistance. There was an increase in heart rate with nifedipine which was probably mediated by enhanced sympathetic discharge from the vasodilation (Thames and Kontos, 1970). Even the patients pre-treated with atenolol had an increase in heart rate although the absolute values were considerably lower. This may be due to the competitive blockade of beta-receptors by atenolol being partially overcome by sympathetic discharge (McDevitt, 1979).

Nifedipine has been shown to have negative inotropic effects in isolated heart muscle preparations (Fleckenstein et al, 1972) but the compensatory sympathetic discharge from the reduction in blood pressure may be masking an intrinsic negative inotropic action of the drug. Indeed Aoki et al (1978) have suggested that nifedipine does have such a "controlled negative inotropic effect" on the heart although they did not make any measurement of this. Joshi and co-workers (1981) examined this problem in 12 patients with ischaemic heart disease undergoing cardiac catheterisation. All had received atenolol prior to the study and measurements were made with a fixed
paced heart rate at 100 bpm. They noted small increases in ejection fraction and mean circumferential fibre shortening but the left ventricular peak dP/dt and peak (dP/dt) x P^{-1} were depressed showing a negative inotropic effect. Our own observations in this hypertensive group are in agreement with this conclusion. The ejection phase indices (ejection fraction, rate of ventricular emptying (DV/Dt) and ratio mean ejection time (MET) to left ventricular ejection time) were all markedly influenced by acute changes in afterload and therefore unhelpful in assessing changes in contractility. Again using the relationship between end-systolic pressure and volume (see chapter 5) we were able to show that the reduction in blood pressure with nifedipine was accompanied by increase in end-systolic volume when the sympathetic activity was blocked by atenolol (fig 31). When nifedipine was given to the patients not pre-treated with atenolol, there was a fall in end-systolic volume with the fall in blood pressure. This is compatible with increased sympathetic activity as evidenced by the increase in heart rate and a compensatory increase in contractility. The negative inotropic effect of nifedipine must be fairly small as it led to no limitations to exercise with the protocol used in this study and was not associated with any symptoms. However, a negative inotropic effect could be of importance in patients with left ventricular dysfunction. Indeed there are several reports of clinical left ventricular failure developing in such patients (Anastassiades, 1980; Robson and Vishwanath, 1982).

In these hypertensive patients the haemodynamic response to upright
bicycle exercise as conventionally assessed by heart rate, blood pressure and cardiac output response was essentially normal with all three increasing. However, in both the untreated and the group pre-treated with atenolol, the end-systolic volume response to exercise with abnormal increase rather than the more characteristic fall (Slutsky et al, 1979; Vojacek et al, 1982) which we observed in a group of normal subjects (see chapter 4). The rise in blood pressure on exercise was unlikely to have been the cause of this abnormal response because nifedipine did not correct the abnormality. In this context it seems more likely that the stress on the heart during exercise makes it more easy to detect an abnormality of cardiac function in hypertension. Although none of our patients had evidence of hypertensive heart disease by WHO criteria, there is evidence as discussed in chapter 1 that the left ventricle shows abnormalities very early in the development of hypertension (Fouad et al, 1980). In a previous study nifedipine had been shown to cause hypotension during head-up tilt (Magomettschnigg, 1983) but our own results show that when exercising even in the upright position there was no hypotensive response to exercise.

Our patients experienced no adverse reaction to nifedipine or the combination of nifedipine and atenolol. As the drugs potentiate each other with respect to the hypertensive effect as shown in this acute study, the combination has obvious advantages. Nifedipine has been used safely in the treatment of angina for long periods (Terry, 1982) and this is of considerable importance when long-term treatment for hypertension is considered with concern being expressed over the
long-term safety of diuretics (Medical Research Council Working Party, 1985) and beta-blocking agents (Oliver, 1982). Alternative drugs are required for the management of hypertension and nifedipine would appear to be suitable (Lederballe Pederson and Michelsen, 1978; Murphy et al, 1983; Wathen et al, 1986) although a similar drug without any negative inotropic effect might be preferable.
ACUTE EFFECTS OF THE CALCIUM ANTAGONIST FELODIPINE IN PATIENTS WITH ESSENTIAL HYPERTENSION

INTRODUCTION

Felodipine is a dihydropyridine compound similar in structure to the calcium channel blocking agent nifedipine (Meyer et al, 1983) and in animals it has been shown to have selectivity for arterial smooth muscle (Ljung, 1980). Studies in normal subjects and patients with coronary artery disease have shown significant arteriolar dilation (Tweddel et al, 1981; Johnsson et al, 1983). The acute effects of felodipine on myocardial contractility or venous vessels in hypertensive subjects have not previously been studied but are important factors in a drug intended for the treatment of high blood pressure. It was felt necessary to establish whether there was any negative inotropic action such as that seen with nifedipine in the previous study. Further, the dose required to produce a clinically important lowering of blood pressure in hypertension was not established, making it necessary to study the effects of two dose levels of the drug.

Patients

Fourteen patients aged 30 - 65 years (mean 54.5 years) with WHO stage 1 essential hypertension were investigated. No patient had clinical or exercise electrocardiographic evidence of ischaemic heart disease. Eight patients had been newly diagnosed and received no treatment
prior to the investigation and a further 6 patients were selected because they had been maintained on atenolol 100 mg daily for a period of greater than a month prior to the study and despite this, their hypertension had not been adequately controlled.

Methods
The patients were studied fasting and supine in a room at 22°C. Control measurements were made after 30 minutes of acclimatisation. The heart rate was monitored continuously by electrocardiograph and blood pressure was recorded by an independent observer using a random zero sphygmomanometer (diastolic phase V). Left ventricular ejection fraction, and changes in cardiac volumes were measured using radionuclide techniques described (chapter 3), including the peripheral scintillation counter for detecting changes in peripheral vascular (venous) volume. For this study, red blood cell labelling was used (Millar et al, 1983) because of the time required to make the observations at the two felodipine dose levels (see fig 32).

Drugs
Felodipine was given initially in a dose of 0.05 mg/kg body weight as an oral solution and its effect observed over 90 minutes, then a further increment of 0.1 mg/kg was given 180 minutes after the first dose with further assessments for one hour. Plasma sampling for felodipine was carried out before, 30 and 60 minutes after each administration. Felodipine was assayed by gas liquid chromatography (Ahnoff, 1984).
Fig 32  Plasma concentration of felodipine in 11 hypertensive patients after 0.05 mg/kg of oral solution at $t = 0$ and a further 0.1 mg/kg $t = 180$ minutes.
Study period

Heart rate and calf counts from the peripheral detector were recorded continuously. Blood pressure was recorded every 5 minutes and radionuclide studies were performed before, 30 and 60 minutes after each dose of felodipine.

Statistical methods

For comparison of the data between groups the values are expressed as mean ± SEM.

Data were analysed by the Student's 't' test for paired data. Values of p > 0.05 were considered not significant.

RESULTS

Blood pressure for the untreated group was 169/102 ± 7/3 mmHg and those on atenolol was slightly lower 159/95 ± 5/4 mmHg. Heart rate was 76 ± 5 bpm in the untreated group and lower as expected (57 ± 4 bpm) in the atenolol treated group. Resting left ventricular ejection fraction was similar for both groups (untreated 0.51 ± 0.02, beta-blocker 0.51 ± 0.03).

Effect of felodipine

Plasma levels of felodipine following administrations are shown in figure 32. The maximum effects were observed within 60 minutes of the oral dose and there was no significant difference in the cardiovascular effects between the two dosage levels despite the
Fig 33 Changes in heart rate (HR), mean arterial pressure (MAP), left ventricular ejection fraction (LVEF), cardiac output (CO) systemic vascular resistance (SVR) and peripheral venous volume (PVV) in 8 previously untreated essential hypertensives (▲) and 6 taking atenolol therapy (●) 30 and 60 minutes after taking 0.05 mg/kg oral felodipine compared with control measurements (C) (x ± SEM).
The effects of a further 0.1 mg/kg felodipine given at \( t = 180 \) minutes on HR, MAP, LVEF, CO, SVR and PVV at 210 and 240 minutes in 8 untreated hypertensive patients (▲) and 6 treated with atenolol (●) (x ± SEM). (See figure 37 for comparison).
differences in the plasma felodipine level achieved (figs 33 and 34). The results for both groups are summarised in table 18.

Previously untreated group
Blood pressure fell with felodipine from 169/102 ± 6/3 mmHg to 132/78 ± 9/5 mmHg after 60 minutes (fig 33). Heart rate increased by 9.5 ± 1.7 bpm (p < 0.01). Left ventricular ejection fraction increased from 0.51 ± 0.02 to 0.59 ± 0.03 (p < 0.01). Cardiac output increased by 30 ± 4% (p < 0.001) but stroke volume was only increased by 12 ± 6% (p < 0.05). End-diastolic volumes were unchanged but end-systolic volume increased by 17 ± 4% (p < 0.05). The calculated systemic vascular resistance fell by 37 ± 5% (p < 0.001) but there was no significant change in the venous volume of the calf.

Atenolol treated group
Given the lower resting heart rate, the response to felodipine was similar (fig 33). For these patients the blood pressure fell by 33/18 ± 7/3 mmHg (p < 0.01) at 60 minutes and the heart rate increased by 7 ± 2 bpm (p < 0.05). Left ventricular ejection fraction increased by 0.06 ± 0.02 (p < 0.01). Cardiac output increased by 55 ± 13% (p < 0.01) and stroke volume increased by 31 ± 11% (p < 0.05). There was a greater fall in systemic vascular resistance of 43 ± 8% (p < 0.01). Again there was no change in the venous volume of the calf.

Pressure-volume relationship
By plotting the end-systolic volume change against the change in
systolic blood pressure as described by Sagawa et al (1977) it can be seen that there is no change in the slope of the line between the untreated and the beta-blocked group (see figure 35).
Relationship between systolic blood pressure (as an approximation of left ventricular end-systolic pressure) and percentage change in end-systolic volume (ESV) with felodipine in untreated hypertensive patients (solid line) and those taking atenolol (dotted line). The lines are parallel suggesting that felodipine has no negative inotropic effect.

(Compare with nifedipine - figure 31).
DISCUSSION

These results confirm that felodipine is a potent vasodilator reducing arterial tone without any apparent effect on venous tone. The results also suggest that an oral dosage of 0.05 mg/kg, which produces blood levels of 10-15 nm/l is probably near the top end of the dose-response curve in hypertensive patients.

The reduction in peripheral vascular resistance is probably responsible for the other haemodynamic changes. The increase in heart rate, stroke volume and ejection fraction have been mediated by the reduction in afterload. This response in hypertensive subjects are similar to those previously seen in normal subjects and patients with coronary artery disease (Tweeddel et al, 1981; Johnsson et al, 1983) although in these other studies systolic blood pressure was not reduced as a result of compensatory mechanisms to maintain blood pressure. It is of interest to note that the increment in heart rate and stroke volume was not abolished in the patients pre-treated with atenolol.

As discussed in the previous study, nifedipine has been shown to have a negative inotropic action but in vitro studies using isolated portal vein, which behaves similarly to small resistance vessels, have suggested that felodipine might have greater selectivity to the arterial circulation (Ljung, 1980). It was for this reason that we chose to compare the effects of felodipine in patients on no previous therapy with those already pre-treated with atenolol. Our results
suggest that the response to felodipine is very similar in those patients treated with adrenoreceptor blockade and those without (figs 33 and 34). In this study we only measured relative changes, so it is impossible to determine whether the slightly greater increase in cardiac output and stroke volume and the fall in peripheral vascular resistance seen in patients on atenolol was due to this group having a higher resting arterial vascular tone but this would be consistent with the known effects of beta-blockade (see chapter 5). The increase in heart rate with felodipine was not prevented by atenolol and could be due to withdrawal of vagal tone or a direct myocardial effect. Again by exploring the relationship between end-systolic blood pressure as an approximation of left ventricular end-systolic pressure and relative left ventricular end-systolic volume an assessment of contractile state could be made (Sagawa et al, 1977; see chapter 5). The two groups of patients showed a similar response (fig 35) suggesting that the contractile state was not altered by felodipine even in the presence of atenolol. This result contrasts with that noticed for nifedipine (fig 31) in the previous study.

In our study there was no demonstrable effect on venous tone such as we have previously observed with glyceryl trinitrate (see chapter 3). In fact, in a group of patients with heart failure, felodipine has been shown to improve systemic and coronary circulatory haemodynamics without impairing the contractile function of the heart (Timmis et al, 1984). These investigators noticed a fall in left ventricular end-diastolic pressure with felodipine which was probably mediated by
reduction in preload although the authors point out that they were unable to exclude venous pooling. Although it is possible that in certain situations where venous tone is increased such as in heart failure (Timmis et al, 1984), felodipine may have an effect on the venous bed, there was no evidence of this in our study of hypertensive subjects.

In this study felodipine had a potent antihypertensive action both when used alone and in beta-blocked patients and this effect was brought about by arterial vasodilation. In contrast to nifedipine there was no evidence of a negative inotropic effect and we were unable to detect any change in the peripheral venous bed. Caution should be applied in extrapolating this study to long-term treatment. However, the results suggest that the combination of felodipine and a beta-blocking agent may be a potent means of controlling severe hypertension.
THE COMPARISON OF FELODIPINE AND MINOXIDIL IN THE TREATMENT OF SEVERE HYPERTENSION

INTRODUCTION

Despite modern drug treatment the management of true drug resistance of hypertension remains a problem in clinical practice. As discussed in Chapter 1 vasodilators are usually added to a regime of beta-blocker and thiazide diuretic when these alone are ineffective. In one controlled trial of such 'third line' therapy, minoxidil was shown to be the most effective but least well tolerated by a group of hypertensive patients (McAreavey et al, 1984). Unfortunately this comparative trial did not contain a limb with calcium antagonist therapy. It has been our practice to restrict the use of minoxidil to male patients who have failed to respond to other third line vasodilators such as hydralazine, prazosin or nifedipine despite good compliance suggesting at least to us that nifedipine is less potent. I was interested in recent reports that felodipine might be more powerful in the treatment of hypertension (Herlitz et al, 1983; Aberg et al, 1985; Collste et al, 1985) and encouraged by the results of the previous acute study. I therefore decided to carry out a crossover trial to compare these two agents in the management of a group of severe hypertensive patients.

Drugs trials in severe hypertensives have ethical difficulties because of the increased risks of stroke and other hypertension-related diseases if the patients are untreated over any length of
I therefore designed a crossover trial after a short dose-titration period so as to avoid difficulties of untreated high blood pressure. It was, however, necessary to have a short, closely observed withdrawal drug period to confirm that the drugs were having an antihypertensive effect.

Patients and Methods

Seventeen hypertensive men (46 - 67 years) who attended the Royal Infirmary out-patient hypertension clinic were studied. All suffered from WHO stage III hypertension with end organ damage in the form of stroke, retinopathy, left ventricular hypertrophy and/or renal failure at the time of presentation. On therapy with Atenolol, a thiazide diuretic and hydralazine, prazosin or nifedipine their diastolic blood pressure had remained greater than 115 mmHg and all had eventually been controlled with a combination of Atenolol 50-100 mg daily, Frusemide 40-160 mg or Bumetanide 1-3 mg daily and Minoxidil 10-45 mg daily. Because of side effects from Atenolol, one patient took Labetalol 800 mg daily. Beta-blockade was confirmed in all patients by a reduction in heart rate on exercise. Patients were excluded if they had suffered a myocardial infarction within 3 months prior to the study, had severe angina pectoris, uncompensated heart failure or other severe concomitant disease. The patients were also excluded if they had evidence of poor compliance or poor clinic attendance.

Measurement of blood pressure

The blood pressure was measured by a single observer using a Hawskley
random zero sphygmomanometer, the readings being taken five minutes after lying supine and one minute after standing.

**Observations**

In addition to heart rate and blood pressure, body weight was measured at each clinic visit along with ankle circumference and evidence of pitting oedema was sought. Adverse reactions were sought in two ways; firstly, by spontaneous comments recorded by the patient at each clinic visit and, secondly, by the doctor's enquiry about side effects which was confined to a standard question (since we last met have you been bothered by any symptoms which are out of the ordinary for you?). Prior to entry and at the end of each limb of the crossover, electrocardiogram, full blood count, serum urea, electrolytes, creatinine and liver function tests were measured. Urinalysis was performed at each clinic visit. To assess compliance, tablets were prescribed in blister packs and tablet counts were performed at each clinic visit. Plasma atenolol levels were also measured by high performance liquid chromatography at each visit. The optimal dose of minoxidil had been already established in clinical dose titration and all patients were considered to have achieved satisfactory control of blood pressure. The mean of three blood pressure recordings taken on three consecutive clinic visits prior to the study were taken as a target blood pressure for the subsequent dose titration of felodipine. Minoxidil was withdrawn and placebo "felodipine" prescribed, other therapy being left unchanged throughout the study. Patients were observed very closely for two weeks and if there was a rise in systolic or diastolic blood
pressure was greater or equal to 15 mmHg, active treatment was begun. At the end of two weeks, or with this rise in blood pressure, the patient was prescribed active felodipine 5 mg twice daily and dose titration was commenced at weekly intervals, increasing to 10 mg and 20 mg twice daily to achieve the individual's target pressure or until significant side effects appeared. Once optimal dosing had been achieved, patients were randomised double-blind to a 6 week treatment with minoxidil or felodipine at the pre-determined optimal doses. The response to therapy was ascertained at 3 and 6 weeks. At the end of the 6 week period, the alternate drug was administered for a further 6 weeks.

Statistical analysis
Data is presented as the mean plus standard deviation. Statistical analysis was carried out by Wilcoxon Rank Sum Test. Values of p > 0.05 were considered not significant.

RESULTS

Deaths and withdrawal
One patient died during initial dose ranging phase. The history and electrocardiogram suggested anterior myocardial infarction with left ventricular failure but autopsy permission was not granted. His blood pressure had been measured at a clinic visit two days prior to his death and was little different (144/94 mmHg supine) from previous recordings on minoxidil (160/90 mmHg). One further patient suffered a possible small subendocardial myocardial infarction when taking
felodipine and was withdrawn. However, four months later he still required minoxidil to control his hypertension and he was therefore re-entered into the study. His subsequent progress was uneventful and he has remained well on felodipine. One patient withdrew from the study because he found the regular clinic attendances too difficult. There were thus 15 patients who completed both limbs of the study. The patients were all accustomed to the hirsutism and two were able to tell which drug they were taking from the heavy growth. Tiredness and headaches were slightly more common on minoxidil and 'dizziness' on felodipine but the total number of complaints were few.

Clinical data

The results are summarised in table 19.

The mean supine blood pressure readings on standard triple antihypertensive therapy were 195/118 ± 20/14 (SD) mmHg, on minoxidil 160/94 ± 20/10 mmHg and when placebo was substituted for minoxidil 171/108 ± 22/12 mmHg (p < 0.01, fig 37). In the dose ranging phase of the felodipine treatment 'target' blood pressure was reached in all patients. Five patients required 5 mg bd of felodipine, 8 patients 10 mg bd (including the patient who died) and 3 patients 20 mg bd). In the crossover study there was no significant difference between the supine blood pressure on felodipine (150/88 ± 19/8 mmHg) compared with minoxidil (148/87 ± 23/11 mmHg, fig 38). The erect blood pressure readings also showed no significant difference and hence the postural fall in blood pressure was the same on both
Fig 36 Supine and erect blood pressures for patients on standard triple antihypertensive therapy (STT), a minoxidil based regimen (minoxidil), after withdrawal of the minoxidil (placebo) and after adding felodipine (felodipine).
Fig 37  Supine (open) and erect (hatched) blood pressures for patients on the minoxidil (M) and felodipine (F) based regimes at 3 and 6 weeks.
regimes (fig 38). Supine heart rate on felodipine was $63 \pm 7$ bpm whilst on minoxidil it was $69 \pm 11$ bpm ($p < 0.05$). Erect heart rate was also significantly higher on minoxidil ($p < 0.05$, table 19). The mean weight on felodipine was $79.9 \pm 13.1$ Kg whilst on minoxidil it was $81.4 \pm 13.3$ Kg ($p < 0.01$). Ankle circumference at the end of 6 weeks on minoxidil was $22.1 \pm 1.57$ cm and was $22.2 \pm 1.71$ cm after 6 weeks of felodipine therapy (NS).

Results of laboratory variables

No significant change in plasma electrolytes, urate, creatinine or urea concentrations were observed during the study. There was a small but significant rise in plasma alkaline phosphatase ($p < 0.01$, table 20) on felodipine and gamma glutamyl transferase was also higher ($p < 0.01$, table 20). Bilirubin, alanine aminotransferase, aspartate aminotransferase and plasma proteins were not changed. The random plasma glucose was also unchanged.
DISCUSSION

The effectiveness of minoxidil in the management of patients with severe hypertension irrespective of aetiology has been proven (Felts and Charles, 1980; McAreeavey et al., 1984; Mackay et al., 1981). Controlled trials have shown it to be more effective than hydralazine and other commonly used third line drugs (McAreeavey et al., 1984; Gottlieb et al., 1972; Conner et al., 1976). However, sodium and water retention, hirsutism (McAreeavey et al., 1984) and the occasional occurrence of pericarditis or pericardial effusion (Campese et al., 1979; Martin et al., 1980) limits its widespread use. In this study blood pressure rose when placebo tablets were substituted for minoxidil showing that this drug was exerting significant antihypertensive action. Blood pressure was equally well controlled with felodipine as minoxidil. The study was designed to show that felodipine could replace the established drug minoxidil and indicates that it could be used as an alternative in severe hypertension. Indeed there is some evidence from this study that it might be preferable because of the considerable adverse effects of minoxidil (Campese et al., 1979; Martin et al., 1980; Mackay et al., 1981). A study of this design where felodipine was compared to a powerful established antihypertensive regimen was considered necessary for ethical reasons.

Ankle circumference was no different on the two drug regimens but ankle swelling with both drugs may be due to a direct vasodilator effect on arterioles and increased capillary pressure. The
significant loss of weight whilst on the felodipine based treatment suggests that fluid retention was less marked than when on minoxidil. Zins (1974) has suggested that minoxidil increased proximal tubular reabsorption of sodium. In contrast preliminary studies with felodipine have suggested a mild diuretic and natriuretic action (Edgar et al., 1985; Leonetti et al., 1985) and this has been attributed to an action on the distal nephron (Di Bona, 1985). Patients taking minoxidil usually require potent diuretics to avoid fluid retention (Campese et al., 1979; Mackay et al., 1981) as our patients did. This may be unnecessary with felodipine and indeed following the trial we were able to reduce the diuretic dosage in patients continuing on felodipine therapy.

Changes in plasma levels of liver derived enzymes have been noted in one other small study of severe hypertension (Collste et al., 1985) but have not been noted in larger studies of patients with less severe hypertension (Personal communication, Hassle). However, it appears that the changes do relate to felodipine therapy because the cross-over study design would tend to exclude other factors, such as alcohol consumption. From the available data it is not possible to determine the aetiology of this derangement but the enzyme pattern would suggest a degree of cholestasis. Calcium antagonist drugs are known to affect gastrointestinal smooth muscle contraction (Malagelada et al., 1984), and this may be true of felodipine on the biliary tree. These 15 patients have now been continued on felodipine therapy for at least 1 year and there has been no deterioration in their liver function assessed by blood enzyme
Development of angiotensin-converting enzyme (ACE) inhibitors has provided an alternative approach to the management of severe hypertension (Edwards and Padfield, 1985). However, it is in this group of patients with severe or complicated hypertension that most of the adverse effects of ACE inhibitors are seen (Cooper, 1983; Stumpe et al, 1984). Indeed, Cooper (1983) has shown that the incidence of neutropaenia associated with captopril rises from 0.02% to 7.2% in patients with complicated hypertension and renal failure. There is also concern about the development of proteinuria in this group of hypertensive patients treated with ACE inhibitors as this may reflect renal damage (Captopril Collaborative Study Group, 1982). ACE inhibitors are, therefore, probably unsuitable at least in some patients with severe hypertension, and felodipine which did not appear to have any serious adverse effects in our small group of patients may be a useful alternative. Studies of large numbers of patients are required.

In summary when compared with standard treatment of minoxidil in severe hypertension felodipine has been shown to be equally effective and well tolerated over a period of 6 weeks. It appears to be associated with less fluid retention and it seems to be a promising drug for use in severe hypertension. However, longer term trials will be required to confirm this.
CONCLUSIONS

In the non-invasive studies of calcium antagonists in this chapter the cardiovascular changes produced by these drugs has been examined. Following the results of acute studies a trial of felodipine was carried out in a group of severe hypertensives because of the difficulties in treating these patients effectively with currently available therapy and the promising results obtained with felodipine in the acute study.

Whilst the negative inotropic action of nifedipine could be demonstrated in intact man our group of hypertensive patients showed no adverse effects related to this, even on exercise. The benefit of combined beta-adrenergic antagonist and calcium antagonist drugs on blood pressure was demonstrated. In contrast to nifedipine, felodipine a new dihydropyridine compound, was shown to have a powerful antihypertensive effect, and no demonstrable negative inotropic action or venous effect. In a trial of chronic therapy in severe hypertension, felodipine was found to be effective and well tolerated. Calcium antagonist therapy appears to have an important role in the management of hypertension and felodipine may be particularly useful in severe cases.
The clinical studies of the circulation described in this thesis were carried out after the development and validation of suitable non-invasive radionuclide methods for assessing the heart and peripheral circulation. As clinical benefit cannot be determined by acute studies this was investigated by appropriate clinical trials. The results of these studies have been discussed individually in detail and the clinically important findings of this work is summarised below.

Normal subject studies
Cardiac function was studied non-invasively in 59 normal subjects at rest and during supine bicycle exercise. The data obtained was broadly comparable with that published by other investigators. However, the differences which have been observed between laboratories including our own can largely be explained by the selection of population samples for study. I chose men from the local community who had not presented to medical attention and were sufficiently young to avoid the data being materially altered by underlying occult ischaemic heart disease. This data, which has not been previously available for a relatively young population, did suggest that there was a true aging effect on cardiac function independent of ischaemic heart disease. As age increased, the rise in cardiac output on exercise was increasingly dependent upon increasing left ventricular end-diastolic volume and stroke volume as the end-systolic volume increases. For this reason changes in
cardiac function on exercise which have been described as "normal" by previous investigators notably the reduction in end-systolic volume, were found to be less reliable predictors as age increased.

Comparison of this normal population with a group of men with a clinical history of angina pectoris showed that there was a very considerable degree of overlap of the cardiac response to exercise between the two groups such that exercise ventriculography could not detect specific cardiac abnormalities in men with angina pectoris selected from the community. However, in the group with angina there were men with evidence of left ventricular dysfunction on exercise and follow-up of this group may determine if this is of prognostic value.

**Studies of heart failure**
Right ventricular function was assessed by radionuclide techniques but whilst measurement of right ventricular ejection fraction was reproducible this method of assessing right ventricular function was found to vary with time such that it was not possible to use this assessment for chronic studies. The acute studies of the effects of sodium nitroprusside and the beta-agonist pirbuterol on the pulmonary circulation in patients with cor pulmonale suggested that combined beta_1 and beta_2 agonist therapy with pirbuterol lowered pulmonary vascular resistance largely by increasing cardiac output and was not associated with reduced arterial oxygenation. This was in contrast to the effects produced by sodium nitroprusside which reduced pulmonary artery pressure and had little effect on cardiac output.
Oral pirbuterol had some selectivity for the pulmonary circulation but this was not seen with sodium nitroprusside. These cardiovascular effects of pirbuterol might prove beneficial in patients with cor pulmonale and the encouraging results obtained suggest that further investigation of this drug is merited.

In view of the poor prognosis of patients with right heart failure such developments, which show that improvement is possible, are to be welcomed.

Studies of hypertension
In the studies of essential hypertension it was shown that although blood pressure was lowered by the beta-adrenergic blocking agent atenolol this was brought about through lowered cardiac output and without any reduction in the elevated peripheral vascular resistance. There is no direct evidence that this is undesirable but from consideration the underlying pathophysiology it does not seem to be ideal. Further, the failure of effective antihypertensive therapy to reduce cardiovascular morbidity and mortality in hypertensive subjects remains unexplained. More precise correction of the cardiovascular abnormalities with antihypertensive therapy might prove beneficial in this respect and this hypothesis requires further investigation.

Calcium antagonist therapy was evaluated and the new dihydropyridine felodipine was shown to be a particularly powerful antihypertensive agent producing a marked reduction in peripheral vascular resistance.
It appeared to have advantages over nifedipine in that whilst nifedipine had a negative inotropic action when the drug was combined with beta-blockade this was not so with felodipine.

As there was sufficient evidence from the acute studies to suggest that felodipine might be particularly useful in the management of severe hypertension, a clinical trial was carried out to evaluate felodipine in this group of patients. Felodipine was found to be at least as effective as the potent vasodilator, minoxidil, and associated with less fluid retention. Although severe hypertension is relatively uncommon it is this group of patients who can potentially derive the maximum benefit from effective antihypertensive therapy. The therapy used to date in this group of patients has been associated with significant adverse effects but follow-up of our patients with severe hypertension has suggested that felodipine may have an important role in the management of this condition.

A rational clinical approach to evaluation of therapy such as that illustrated in this thesis is required and should improve the treatment of cardiovascular diseases.
CARDIOVASCULAR DISEASES ARE THE GREATEST CAUSE OF MORBIDITY AND PREMATURE MORTALITY IN MOST WESTERN COUNTRIES. MANY DRUGS HAVE BEEN DEVELOPED FOR USE IN THIS GROUP OF CONDITIONS, NOTABLY HEART FAILURE AND HYPERTENSION. WITH THE USE OF THESE AGENTS THERE HAS CLEARLY BEEN AN IMPROVEMENT IN PROGNOSIS IN PATIENTS WITH MORE SEVERE FORMS OF HYPERTENSION THROUGH REDUCTION IN STROKE AND RENAL FAILURE. THERE ARE ALSO SUGGESTIONS FROM VERY RECENTLY REPORTED STUDIES OF HEART FAILURE THAT PROGNOSIS MAY BE IMPROVING IN SOME PATIENTS. HOWEVER, THE PROGRESS HAS BEEN SLOW AND MUCH WORK IS NEEDED SO THAT THERAPY CAN BE OPTIMISED TO IMPROVE PROGNOSIS AND REDUCE UNWANTED SIDE EFFECTS. THE RATIONAL USE OF CARDIOVASCULAR DRUGS DEPENDS UPON AN UNDERSTANDING OF THE CIRCULATORY DERRANGEMENTS IN THE VARIOUS CARDIOVASCULAR DISEASES AND KNOWLEDGE OF HOW THESE MIGHT BEST BE IMPROVED. IN THIS DISSERTATION DRUGS WHICH AFFECT INOTROPIC STATE AND VASODILATORS HAVE BEEN STUDIED, BOTH BY EXAMINATION OF THEIR CARDIOVASCULAR EFFECTS AND WHERE APPROPRIATE BY CAREFULLY DESIGNED CLINICAL TRIAL. THESE STUDIES ILLUSTRATE THIS APPROACH TO CLINICAL EVALUATION OF DRUG THERAPY AND THE SPECIFIC CONCLUSIONS FROM EACH STUDY HAVE ALREADY BEEN GIVEN. IT WILL, HOWEVER, BE USEFUL TO CONSIDER THE MORE GENERAL IMPLICATIONS OF THIS WORK.

From the work presented in this thesis it is apparent that using radionuclide methods the effects of drug action on the central and peripheral circulation can be assessed. Because the techniques are non-invasive and have a high degree of patient acceptability they are
suitable for studying larger groups of patients and those with less severe forms of disease. The studies which have been presented illustrate the ways in which the cardiovascular effects of drugs in man can be elucidated using those non-invasive techniques.

The main concern about radionuclide studies is the radiation burden to the patient. Using gamma emitting isotopes with a short half-life, such as $^{99m}$technetium this is not great. For the studies described in this thesis, which are typical of those required for nuclear cardiology, the radiation dosage to each patient was somewhat less than that required for contrast radiological procedures such as intravenous urography. Although no adverse effects have been demonstrated in patients receiving these doses of gamma radiation, it would be difficult to notice any minor adverse effects of the isotope on, for example, the incidence of tumours, in the types of population studied. Hence it is prudent to reduce the dose as far as is reasonably possible and avoid studies in women of child-bearing potential. Nevertheless the risks are small compared with other types of investigation and the benefits are potentially large.

Using these methods I have approached the problem of trying to assess contractility. Differentiating between changes brought about by altering the inotropic state of the heart and those which occur as a result of arterial vasodilation in intact man is particularly difficult. A practical method for examining this, based on data from previous invasive studies, has been developed.
This technique has been used in the studies described above and useful information obtained. Because small drug induced reduction in inotropic state may be important in patients with heart failure, and where combinations of cardiovascular drugs are used, such investigation is of value.

The computer software necessary for the cardiovascular studies carried out in this thesis is now being incorporated into many of the commercially available multipurpose gamma camera systems so the facilities for such studies of the heart are widely available. These facilities provide a suitable basis for therapeutic trials where previously such studies have been limited to the few departments with catheter laboratories. This opportunity to study the effects of drug therapy on the circulation should be grasped.

The technique for studying the effects of drugs on the peripheral venous bed described in this thesis deserve particular mention. Many cardiovascular drugs affect the venous system but relatively little attention has been paid to this part of the circulation despite its importance. This must be largely due to the cumbersome, and difficult methodology previously available. The relatively simple non-invasive radionuclide method described is available to any nuclear medicine physician at very little cost and should allow much more extensive study of the effects of the cardiovascular drugs on the peripheral venous bed, carried out simultaneously with other investigations. Further study is required to see if a reliable absolute calibration of this technique can be developed such that
precise quantification of drug actions on the venous bed would be possible.

The radionuclide studies of normal subjects outlined the difficulties in deriving a normal range of cardiac response when there appears to be an ageing phenomenon in the heart. Moreover it was impossible to separate a normal population from one with clinical features of angina using assessments of exercise cardiac function. Perhaps this is not too surprising but it does give an indication of the limitations of such investigations in clinical practice. More strenuous exercise might have led to more patients showing evidence of impaired myocardial function but such levels of exercise would have been very variable and assessment difficult without a very short scanning time, such as can now be achieved with short half-life isotopes and a modern multicrystal gamma camera system. However, such "maximal" exercise protocols when used to study populations in this way are open to the criticism that the results would merely reflect the individual's fitness. It seems unlikely that any measurement of ventricular function is going to replace exercise electrocardiography as a diagnostic tool but this type of assessment is likely to become of increasing value for characterising circulatory abnormalities and tailoring drug therapy to the individual patient's requirements.

In cor pulmonale we were able to show that the effects of a combined beta_1 and beta_2 adrenergic agonist appeared beneficial. The prognosis of patients with this condition is extremely poor. To
date long-term controlled oxygen therapy is the only treatment which has been shown to improve exercise tolerance and prognosis in patients with cor pulmonale but this type of treatment is both expensive and very inconvenient to administer. Hence it would be of considerable value to develop drug treatment for this condition to be used either as an alternative to, or possibly in combination with, oxygen therapy. Further study of the long-term effects of pirbuterol in this group of patients is required. Such a study would probably need to be multicentre in design so that enough patients could be studied to obtain a meaningful result.

Similarly acute studies have previously suggested that inotropic drug therapy might have clinically beneficial circulatory effects in patients with heart failure. As the prognosis in this condition is so poor and orally active inotropic agents are now becoming available, satisfactory clinical evaluation is required. Non-invasive evaluation of drug therapy will allow the study of the effects of these new agents in sufficiently large population groups to produce meaningful data. It is important to realise that effective therapy of this common condition may be available for those patients who are not adequately controlled by diuretic therapy. As possibly 1% of the population are under medical care for heart failure effective therapy for this condition is an important goal.

Hypertension is another common condition where the risks and potential benefits of treatment are well recognised. The incidence of stroke and renal failure has been reduced by effective
An antihypertensive therapy and the need to reduce the cardiovascular morbidity related to hypertension is paramount. It seems unlikely that present therapy with beta-adrenergic blocking agents and diuretics is going to achieve this. Whilst the reasons for this is not clear, more precise correction of the circulatory abnormalities in hypertension would seem to be one of the best ways of approaching the problem. Calcium antagonist agents may have a role in this regard and the differences in vascular selectivity between the various calcium antigens may be important. Felodipine appeared a suitable agent. It was shown to have some selectivity towards the arterial tree, no adverse effects on myocardial function and its use has been associated with fewer adverse effects than standard therapy. In view of the common occurrence of adverse effects with current antihypertensive medication and the long-term nature of this type of treatment, a reduction in drug related problems must be a major aim of drug development. This will also depend upon using drugs with a greater specificity for the desired therapeutic effect. Further development towards correction of the circulatory abnormalities in hypertension, possibly with selective calcium antagonists should prove very beneficial and may reduce the cardiovascular morbidity associated with this condition.

Selection of those areas of work which might prove most rewarding is an important aspect of any research programme. In the case of cardiovascular disorders, this requires characterisation of the circulatory abnormalities which require correction in the disease in question and identification of those drugs which will best correct
these. These drugs then require adequate clinical evaluation. In this way treatment policies will advance and hopefully reduce the morbidity and mortality of cardiovascular disease.
### TABLE 1

**EJECTION FRACTION RESULTS WITH VANDERBILT CARDIAC PHANTOM**

<table>
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<th>Simulated Heart rate (bpm)</th>
<th>Low (0.25)</th>
<th>Medium (0.50)</th>
<th>High (0.75)</th>
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<td>0.34</td>
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<td>0.89*</td>
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20 m sec data collection periods

* Data from Tonge et al (1986)
### TABLE 2

**INTER STUDY AND INTER OBSERVER (WJH and CGW)**

REPRODUCIBILITY OF LEFT VENTRICULAR END-DIASTOLIC COUNT RATE AND LEFT VENTRICULAR EJECTION FRACTION (LVEF)

IN 15 PATIENTS

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<th>Study</th>
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<th>LVEF</th>
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TABLE 2 (cont'd)

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<th>Study</th>
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<td>CGW</td>
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<td>30546</td>
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</table>

* no decay clearance correction

LVEF - mean inter-study difference 0.02
- mean inter-observer difference 0.01
TABLE 3

REPRODUCIBILITY OF RIGHT VENTRICULAR EJECTION FRACTION
IN PATIENTS WITH CHRONIC BRONCHITIS

<table>
<thead>
<tr>
<th>Patient</th>
<th>FEV\textsubscript{1} (l)</th>
<th>FVC (l)</th>
<th>RVEF 1st Measurement</th>
<th>RVEF 2nd Measurement</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>2.10</td>
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<td>0.17</td>
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<td>0.45</td>
<td>1.25</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
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<td>6</td>
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<td>1.77</td>
<td>0.44</td>
<td>0.47</td>
</tr>
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<td>2.50</td>
<td>0.44</td>
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<td>1.10</td>
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<td>0.25</td>
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<td>3.60</td>
<td>0.24</td>
<td>0.26</td>
</tr>
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<td>0.90</td>
<td>1.40</td>
<td>0.41</td>
<td>0.41</td>
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<tr>
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<td>1.65</td>
<td>0.53</td>
<td>0.55</td>
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<tr>
<td>12</td>
<td>1.20</td>
<td>2.40</td>
<td>0.45</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Mean | 0.35                | 0.34                |
SD   | 0.13                | 0.15                |

Mean difference 0.03
TABLE 4

REPRODUCIBILITY OF LVEF AND RVEF IN 12 PATIENTS WITH CHRONIC BRONCHITIS AT BASELINE (WEEK 1) AND 7 DAYS LATER (WEEK 2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVEF Week 1</th>
<th>LVEF Week 2</th>
<th>RVEF Week 1</th>
<th>RVEF Week 2</th>
</tr>
</thead>
<tbody>
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<td>0.55</td>
<td>0.51</td>
<td>0.31</td>
<td>0.40</td>
</tr>
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<td>3</td>
<td>0.58</td>
<td>0.69</td>
<td>0.59</td>
<td>0.62</td>
</tr>
<tr>
<td>4</td>
<td>0.45</td>
<td>0.41</td>
<td>0.40</td>
<td>0.37</td>
</tr>
<tr>
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<td>0.46</td>
<td>0.44</td>
<td>0.44</td>
<td>0.52</td>
</tr>
<tr>
<td>6</td>
<td>0.27</td>
<td>0.27</td>
<td>0.29</td>
<td>0.47</td>
</tr>
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<td>7</td>
<td>0.49</td>
<td>0.48</td>
<td>0.53</td>
<td>0.52</td>
</tr>
<tr>
<td>8</td>
<td>0.46</td>
<td>0.43</td>
<td>0.47</td>
<td>0.36</td>
</tr>
<tr>
<td>9</td>
<td>0.49</td>
<td>0.52</td>
<td>0.56</td>
<td>0.64</td>
</tr>
<tr>
<td>10</td>
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<td>0.25</td>
<td>0.25</td>
<td>0.22</td>
</tr>
<tr>
<td>11</td>
<td>0.27</td>
<td>0.27</td>
<td>0.11</td>
<td>0.10</td>
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<tr>
<td>12</td>
<td>0.29</td>
<td>0.28</td>
<td>0.34</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Mean (SD) 0.42(0.13) 0.42(0.13) 0.40(0.13) 0.41(0.15)

\( r = 0.95 \)  \( r = 0.85 \)

\( p < 0.001 \)  \( p < 0.001 \)
### TABLE 5

**COMPARISON OF FIRST PASS AND EQUILIBRIUM METHODS FOR DETERMINING LEFT VENTRICULAR END DIASTOLIC VOLUME (EDV) AND CARDIAC OUTPUT (CO)**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Weight (kg)</th>
<th>BSA (m²)</th>
<th>LVEF</th>
<th>HR (bpm)</th>
<th>EDV (ml)</th>
<th>CO (l min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>91.7</td>
<td>2.02</td>
<td>0.43</td>
<td>74</td>
<td>247</td>
<td>556*</td>
</tr>
<tr>
<td>2</td>
<td>79.4</td>
<td>1.97</td>
<td>0.09</td>
<td>106</td>
<td>381</td>
<td>350</td>
</tr>
<tr>
<td>3</td>
<td>64.5</td>
<td>1.73</td>
<td>0.32</td>
<td>74</td>
<td>218</td>
<td>117</td>
</tr>
<tr>
<td>4</td>
<td>81.8</td>
<td>1.85</td>
<td>0.42</td>
<td>62</td>
<td>111</td>
<td>112</td>
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<tr>
<td>5</td>
<td>79.7</td>
<td>1.89</td>
<td>0.15</td>
<td>82</td>
<td>282</td>
<td>285</td>
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<tr>
<td>6</td>
<td>88.4</td>
<td>2.02</td>
<td>0.44</td>
<td>78</td>
<td>133</td>
<td>101</td>
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<tr>
<td>7</td>
<td>53.0</td>
<td>1.55</td>
<td>0.24</td>
<td>102</td>
<td>139</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>65.2</td>
<td>1.61</td>
<td>0.25</td>
<td>78</td>
<td>170</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>65.0</td>
<td>1.69</td>
<td>0.55</td>
<td>70</td>
<td>181</td>
<td>139</td>
</tr>
<tr>
<td>10</td>
<td>55.0</td>
<td>1.47</td>
<td>0.52</td>
<td>82</td>
<td>96</td>
<td>107</td>
</tr>
</tbody>
</table>

$r = 0.93$  
$p < 0.01$

$r = 0.71$  
$p < 0.05$

* Excluded from analysis (> 2 SD from mean)
## Table 6

**Comparison of First Pass Radionuclide Determination of Cardiac Output with Thromodilution**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Body surface area (m²)</th>
<th>HR (bpm)</th>
<th>Radionuclide LVEF</th>
<th>Radionuclide CO (1 min⁻¹)</th>
<th>Thermodilution CO (1 min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.78</td>
<td>90</td>
<td>0.54</td>
<td>5.30</td>
<td>3.98</td>
</tr>
<tr>
<td>2</td>
<td>1.68</td>
<td>74</td>
<td>0.61</td>
<td>6.90</td>
<td>5.96</td>
</tr>
<tr>
<td>3</td>
<td>1.43</td>
<td>100</td>
<td>0.16</td>
<td>3.29</td>
<td>2.95</td>
</tr>
<tr>
<td>4</td>
<td>1.92</td>
<td>99</td>
<td>0.18</td>
<td>3.60</td>
<td>3.50</td>
</tr>
<tr>
<td>5</td>
<td>2.02</td>
<td>90</td>
<td>0.79</td>
<td>5.24</td>
<td>5.05</td>
</tr>
<tr>
<td>6</td>
<td>2.10</td>
<td>90</td>
<td>0.60</td>
<td>8.47</td>
<td>8.99</td>
</tr>
</tbody>
</table>

**Mean difference for CO = 0.41 l min⁻¹**
<table>
<thead>
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<th></th>
<th>Control</th>
<th>GTN</th>
<th>Control</th>
<th>Hydralazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>74.9±6.4</td>
<td>85.2±5.3***</td>
<td>71.6±5.5</td>
<td>77.1±6.3**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76±4</td>
<td>77±3</td>
<td>80±3</td>
<td>72±3**</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133±8</td>
<td>128±7*</td>
<td>138±7</td>
<td>126±8****</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.470±0.046</td>
<td>0.503±0.048****</td>
<td>0.447±0.041</td>
<td>0.504±0.040****</td>
</tr>
<tr>
<td>Relative cardiac output</td>
<td>100.0</td>
<td>107±6.6</td>
<td>100.0</td>
<td>116±4.1***</td>
</tr>
<tr>
<td>Relative end-diastolic volume</td>
<td>100.0</td>
<td>82±4****</td>
<td>100.0</td>
<td>93.5±2.7*</td>
</tr>
<tr>
<td>Relative peripheral vascular resistance</td>
<td>100.0</td>
<td>88.9±5.1*</td>
<td>100.0</td>
<td>81.1±3.6****</td>
</tr>
<tr>
<td>Relative calf counts</td>
<td>100.0</td>
<td>109.6±1.5**</td>
<td>100.0</td>
<td>98.0±2.6</td>
</tr>
</tbody>
</table>

Mean group date ± SEM (n = 10)

Significance compared with control

* p < 0.05
** p < 0.01
*** p < 0.005
**** p < 0.001
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<tr>
<th>Subject</th>
<th>Age</th>
<th>Wt</th>
<th>BSA m²</th>
<th>BP</th>
<th>Bruce ETT</th>
<th>Rest HR (bpm)</th>
<th>Ex HR (bpm)</th>
<th>Rest LVEF</th>
<th>75 Watt LVEF</th>
<th>Rest CO (1 min)</th>
<th>75 Watt Ex CO (1 min)</th>
</tr>
</thead>
<tbody>
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<td>29.2</td>
<td>64.0</td>
<td>1.76</td>
<td>110/70</td>
<td>N</td>
<td>67</td>
<td>124</td>
<td>0.50</td>
<td>0.59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>35.1</td>
<td>83.5</td>
<td>1.95</td>
<td>118/66</td>
<td>N</td>
<td>64</td>
<td>110</td>
<td>0.44</td>
<td>0.71</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>27.8</td>
<td>-</td>
<td>-</td>
<td>132/90</td>
<td>N</td>
<td>88</td>
<td>116</td>
<td>0.52</td>
<td>0.58</td>
<td>-</td>
<td>-</td>
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<tr>
<td>4</td>
<td>27.0</td>
<td>100.5</td>
<td>2.26</td>
<td>124/74</td>
<td>N</td>
<td>64</td>
<td>104</td>
<td>0.50</td>
<td>0.57</td>
<td>6.80</td>
<td>14.9</td>
</tr>
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<td>35.1</td>
<td>72.7</td>
<td>1.88</td>
<td>112/80</td>
<td>N</td>
<td>70</td>
<td>116</td>
<td>0.47</td>
<td>0.54</td>
<td>2.99</td>
<td>5.9</td>
</tr>
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<td>65.5</td>
<td>1.79</td>
<td>134/78</td>
<td>N</td>
<td>74</td>
<td>116</td>
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<td>6.9</td>
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<td>1.72</td>
<td>114/74</td>
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<td>1.74</td>
<td>138/84</td>
<td>N</td>
<td>68</td>
<td>116</td>
<td>0.60</td>
<td>0.73</td>
<td>4.02</td>
<td>7.2</td>
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<td>88.8</td>
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<td>N</td>
<td>78</td>
<td>130</td>
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<td>0.49</td>
<td>5.75</td>
<td>11.6</td>
</tr>
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<td>27.0</td>
<td>88.5</td>
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<td>116</td>
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<td>27.7</td>
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<td>1.75</td>
<td>120/70</td>
<td>N</td>
<td>70</td>
<td>116</td>
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<td>0.71</td>
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<td>2.26</td>
<td>142/82</td>
<td>N</td>
<td>88</td>
<td>136</td>
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<td>0.63</td>
<td>6.49</td>
<td>11.99</td>
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</table>
TABLE 8 (cont’d)

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<tr>
<th>Subject</th>
<th>Age</th>
<th>Wt</th>
<th>BSA $m^2$</th>
<th>BP</th>
<th>Bruce ETT</th>
<th>Rest HR (bpm)</th>
<th>Ex HR (bpm)</th>
<th>Rest LVEF</th>
<th>75 Watt LVEF (1 min)</th>
<th>Rest CO (1 min)</th>
<th>75 Watt Ex CO (1 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>28.0</td>
<td>74.4</td>
<td>1.95</td>
<td>124/74</td>
<td>N</td>
<td>70</td>
<td>124</td>
<td>0.53</td>
<td>0.58</td>
<td>5.34</td>
<td>11.80</td>
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<td>33.2</td>
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<td>1.91</td>
<td>136/86</td>
<td>N</td>
<td>78</td>
<td>124</td>
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<td>0.64</td>
<td>4.22</td>
<td>9.03</td>
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<td>74.3</td>
<td>1.88</td>
<td>138/84</td>
<td>N</td>
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<td>110</td>
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<td>110</td>
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<td>9.37</td>
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<td>1.96</td>
<td>126/76</td>
<td>Ab</td>
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<td>110</td>
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<td>0.45</td>
<td>4.79</td>
<td>9.82</td>
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<td>10.1</td>
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</tr>
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</table>

* Subject 17 has been excluded from the analysis
### Table 9

Rest and Exercise Radionuclide Ventriculogram Data Showing Change from Rest with 75W Supine Exercise for Normal Subjects

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Rest LVEF</th>
<th>Ex LVEF</th>
<th>A_1 (%)</th>
<th>A_2 (%)</th>
<th>A_3 (%)</th>
<th>A_4 (%)</th>
<th>ESV (%)</th>
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Correlation with age:
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- $r = -0.11$, $p < 0.01$
- $r = -0.30$, $p < 0.01$
- $r = 0.42$, $p < 0.01$
- $r = 0.09$, $p < 0.01$
- $r = 0.39$, $p < 0.01$
- $r = -0.16$, $p < 0.01$
- $r = -0.51$, $p < 0.01$

Estimated regression slope:
- $0.0007$, $-0.0010$, $-0.0017$, $0.78$, $0.14$, $0.39$, $-0.42$, $-0.43$

Upper confidence limit (95%):
- $0.0027$, $0.0030$, $-0.0004$, $1.23$, $0.49$, $0.63$, $0.39$, $-0.22$

Lower confidence limit (95%):
- $-0.0013$, $-0.0031$, $-0.0031$, $0.33$, $-0.21$, $0.15$, $-1.23$, $-0.63$

* Subjects with positive electrocardiographic exercise test
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<td>-6.41, 4.7</td>
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<tr>
<td>Delta heart rate (bpm)</td>
<td>36.9 (1.28)</td>
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<td>0.3, 9.4</td>
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<tr>
<td>Delta end diastolic volume (%)</td>
<td>10.1 (1.49)</td>
<td>4.5 (2.24)</td>
<td>-10.8, -0.4</td>
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<tr>
<td>Delta stroke volume (%)</td>
<td>24.1 (1.88)</td>
<td>12.8 (2.45)</td>
<td>-17.4, -5.3</td>
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<td>Delta cardiac index (%)</td>
<td>90.1 (4.72)</td>
<td>79.7 (6.08)</td>
<td>-25.4, 4.8</td>
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<tr>
<td>Delta end systolic volume (%)</td>
<td>-5.3 (2.61)</td>
<td>-6.4 (3.86)</td>
<td>-10.1, 7.9</td>
</tr>
<tr>
<td>Author</td>
<td>Number</td>
<td>% over 60 years</td>
<td>Type of Subject</td>
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<td>Iskandrian (1987)</td>
<td>90</td>
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<td>Port et al (1980)</td>
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<td>45</td>
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<td>Rodeheffer et al (1984)</td>
<td>61</td>
<td>34</td>
<td>Community derived after extensive exclusion on screening for heart disease</td>
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<td>Manyari et al (1983)</td>
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<td>Poliner et al (1980)</td>
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<td>Berger et al (1979)</td>
<td>13</td>
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<td>Chest pain Normal coronary angiogram</td>
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<tr>
<td>Patient</td>
<td>Age (yrs)</td>
<td>Wt (kg)</td>
<td>Body surface area (m²)</td>
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<td>-----------</td>
<td>---------</td>
<td>------------------------</td>
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<td>1.95</td>
<td>200/107</td>
</tr>
<tr>
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<td>39</td>
<td>1.93</td>
<td>170/115</td>
</tr>
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<td>50</td>
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<td>225/125</td>
</tr>
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<td>45</td>
<td>1.92</td>
<td>195/120</td>
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<td>61</td>
<td>2.13</td>
<td>155/110</td>
</tr>
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<td>48</td>
<td>1.74</td>
<td>200/115</td>
</tr>
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<td>1.86</td>
<td>160/100</td>
</tr>
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<td>56</td>
<td>1.84</td>
<td>200/120</td>
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</tr>
<tr>
<td>11</td>
<td>50</td>
<td>1.92</td>
<td>155/105</td>
</tr>
<tr>
<td>Mean</td>
<td>50.3</td>
<td>1.91</td>
<td>185/113</td>
</tr>
<tr>
<td>SD</td>
<td>6.3</td>
<td>0.09</td>
<td>23/8</td>
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### TABLE 13

**THE CARDIOVASCULAR EFFECTS OF ATENOLOL IN WHO**

**STAGE I ESSENTIAL HYPERTENSION**

Measured data

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<tr>
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<th>Entry</th>
<th>After treatment</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>74±19.9</td>
<td>62±11.5</td>
<td>11</td>
<td>&lt;0.01</td>
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<td>75W exercise heart rate (bpm)</td>
<td>119±18</td>
<td>92±6.0</td>
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</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>185±23</td>
<td>132±13</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>113±8</td>
<td>86±6</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>136.1±13.0</td>
<td>99.8±6.9</td>
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<td>Cardiac index (l/min/m²)</td>
<td>4.0±0.62</td>
<td>3.4±0.61</td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (rest)</td>
<td>0.53±0.076</td>
<td>0.55±0.070</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (supine)</td>
<td>0.53±0.060</td>
<td>0.55±0.072</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary transit time (sec)</td>
<td>7.5±1.15</td>
<td>8.4±2.21</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Total blood volume (l)</td>
<td>5.37±0.67</td>
<td>5.3±0.79</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Derived data</td>
<td>Entry</td>
<td>After treatment</td>
<td>n=9</td>
<td>NS</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------</td>
<td>-----------------</td>
<td>-----</td>
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</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>55±8.7</td>
<td>55±8.8</td>
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<td></td>
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<tr>
<td>Pulmonary blood volume index (ml)</td>
<td>502±96</td>
<td>460±97</td>
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<td>Ratio pulm/total blood vol</td>
<td>0.185±0.019</td>
<td>0.172±0.021</td>
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<tr>
<td>Peripheral vasc resist index (dyne.s cm⁻⁵m⁻²)</td>
<td>2797±509</td>
<td>2447±591</td>
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### Table 14

**Characteristics of Patients with Cor Pulmonale**

<table>
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<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>FEV₁ (1)</th>
<th>FVC (1)</th>
<th>PaO₂ (kPa)</th>
<th>PaCO₂ (kPa)</th>
<th>SaO₂ (%)</th>
<th>LVEF</th>
<th>RVEF</th>
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<td>1</td>
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<td>0.5</td>
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<td>6.0</td>
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<td>78</td>
<td>0.79</td>
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<td>0.6</td>
<td>1.6</td>
<td>7.1</td>
<td>7.3</td>
<td>84</td>
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<td>0.42</td>
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<td>3</td>
<td>58</td>
<td>0.5</td>
<td>1.5</td>
<td>6.3</td>
<td>6.7</td>
<td>82</td>
<td>0.63</td>
<td>0.42</td>
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<tr>
<td>4</td>
<td>70</td>
<td>0.5</td>
<td>1.4</td>
<td>6.5</td>
<td>6.4</td>
<td>86</td>
<td>0.51</td>
<td>0.47</td>
</tr>
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<td>58</td>
<td>1.3</td>
<td>3.3</td>
<td>8.3</td>
<td>6.3</td>
<td>93</td>
<td>0.64</td>
<td>0.46</td>
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<td>0.7</td>
<td>1.6</td>
<td>8.3</td>
<td>5.7</td>
<td>94</td>
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<td>71</td>
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<td>2.3</td>
<td>7.2</td>
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<td>44</td>
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<td>1.4</td>
<td>7.6</td>
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<td>82</td>
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<td>41</td>
<td>0.7</td>
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<td>6.7</td>
<td>5.2</td>
<td>83</td>
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<td>2.2</td>
<td>8.0</td>
<td>7.1</td>
<td>90</td>
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<td>0.37</td>
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<td>0.8</td>
<td>8.3</td>
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<td>89</td>
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<td>0.58</td>
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<tr>
<td>12</td>
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<td>3.1</td>
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<td>90</td>
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<tr>
<td>Mean</td>
<td>60</td>
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<td>7.3</td>
<td>6.4</td>
<td>87</td>
<td>0.58</td>
<td>0.46</td>
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<td>0.7</td>
<td>0.8</td>
<td>0.7</td>
<td>5</td>
<td>0.09</td>
<td>0.08</td>
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### PLASMA PIRBUTEROL CONCENTRATIONS IN 12 PATIENTS 60 AND 120 MINUTES AFTER ORAL ADMINISTRATION OF THE DRUG

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<thead>
<tr>
<th>Patient No</th>
<th>Dose of pirbuterol (mg)</th>
<th>Plasma pirbuterol (µg/l) 60 min</th>
<th>Plasma pirbuterol (µg/l) 120 min</th>
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<td>1</td>
<td>22.5</td>
<td>-</td>
<td>-</td>
</tr>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>22.5</td>
<td>45.1</td>
<td>34.6</td>
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<td>9.6</td>
<td>35.2</td>
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<td>22.5</td>
<td>43.7</td>
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<td>15</td>
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<td>12</td>
<td>15</td>
<td>34.9</td>
<td>33.9</td>
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**TABLE 16**

**HAEMODYNAMIC DATA FOR PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA RECEIVING SODIUM NITROPRUSSIDE (SNP) AND PIRBUTEROL (mean ± SD)**

<table>
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<th>Control (n=12)</th>
<th>SNP (n=10)</th>
<th>Pirbuterol (n=12)</th>
</tr>
</thead>
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<tr>
<td>Mean heart rate (bpm)</td>
<td>87±13</td>
<td>96±16**</td>
<td>97±15**</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>93±13</td>
<td>72±5***</td>
<td>91±12</td>
</tr>
<tr>
<td>Cardiac index (l m⁻²)</td>
<td>2.62±0.58</td>
<td>2.82±0.60</td>
<td>3.15±0.62***</td>
</tr>
<tr>
<td>Stroke volume index (ml m⁻²)</td>
<td>31±8</td>
<td>28±7***</td>
<td>34±8*</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dyn.s.cm⁻⁵m⁻²)</td>
<td>1819±588</td>
<td>1271±272*</td>
<td>1469±515***</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>30±5</td>
<td>22±6***</td>
<td>27±5*</td>
</tr>
<tr>
<td>Total pulmonary vascular resistance (dyn.s.cm⁻⁵m⁻²)</td>
<td>566±149</td>
<td>400±140***</td>
<td>428±114***</td>
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<tr>
<td>Right ventricular end-systolic pressure (mmHg)</td>
<td>47±9</td>
<td>36±8***</td>
<td>42±10</td>
</tr>
<tr>
<td>Right ventricular end-systolic volume index (ml m⁻²)</td>
<td>38±14</td>
<td>28±11*</td>
<td>29±11*</td>
</tr>
<tr>
<td>Ratio RVESP/RVESV₁</td>
<td>1.4±0.74</td>
<td>1.39±0.67</td>
<td>1.77±1.02*</td>
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<tr>
<td>Systolic blood pressure</td>
<td>126±14</td>
<td>100±10***</td>
<td>123±14</td>
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<tr>
<td>Left ventricular end-systolic volume index</td>
<td>23.5±11.3</td>
<td>15.6±9.2</td>
<td>21.3±10.1</td>
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<tr>
<td>RVEF</td>
<td>0.46±0.08</td>
<td>0.51±0.11</td>
<td>0.55±0.08***</td>
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<td>LVEF</td>
<td>0.58±0.09</td>
<td>0.67±0.10*</td>
<td>0.63±0.10</td>
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</table>

* p < 0.05
** p < 0.01
*** p < 0.001
<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Control Rest</th>
<th>Control Exercise</th>
<th>Nifedipine Rest</th>
<th>Nifedipine Exercise</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>1</td>
<td>85.8 (4.7)</td>
<td>106.6 (4.2)</td>
<td>101.1 (6.3)</td>
<td>124.0 (5.8)</td>
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<td>2</td>
<td>63.7 (2.6)</td>
<td>88.0 (2.1)</td>
<td>71.3 (2.7)</td>
<td>90.0 (2.5)</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>1</td>
<td>152.2 (4.8)</td>
<td>177.5 (6.5)</td>
<td>146.2 (4.4)</td>
<td>167.6 (5.8)</td>
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<tr>
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<td>2</td>
<td>158.3 (4.9)</td>
<td>170.8 (5.9)</td>
<td>127 (6.4)</td>
<td>145.8 (8.0)</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<td>102.9 (2.7)</td>
<td>109.4 (2.8)</td>
<td>89.5 (3.3)</td>
<td>98.5 (2.8)</td>
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<td>100.8 (4.2)</td>
<td>102.8 (4.3)</td>
<td>86.2 (3.9)</td>
<td>94.2 (3.7)</td>
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<td>Ejection fraction (Units)</td>
<td>1</td>
<td>0.61 (0.03)</td>
<td>0.65 (0.03)</td>
<td>0.68 (0.03)</td>
<td>0.69 (0.03)</td>
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<td>0.59 (0.03)</td>
<td>0.58 (0.03)</td>
<td>0.58 (0.02)</td>
<td>0.62 (0.02)</td>
</tr>
<tr>
<td>Relative cardiac output (%)</td>
<td>1</td>
<td>100</td>
<td>178.7 (12.7)</td>
<td>143.9 (9.2)</td>
<td>100.1 (10)</td>
</tr>
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<td>100</td>
<td>196.3 (8.7)</td>
<td>111.2 (9.3)</td>
<td>195.2 (16.5)</td>
</tr>
<tr>
<td>Relative stroke volume (%)</td>
<td>1</td>
<td>100</td>
<td>141.9 (10.7)</td>
<td>122.5 (8.0)</td>
<td>143.8 (12.5)</td>
</tr>
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<td>100</td>
<td>141.5 (3.9)</td>
<td>98.3 (4.5)</td>
<td>136.2 (7.4)</td>
</tr>
<tr>
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<td>Group</td>
<td>Nifedipine</td>
<td>Rest</td>
<td>Exercise</td>
<td>Nifedipine</td>
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<td>-------</td>
<td>------------</td>
<td>------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Relative systemic vascular resistance (%)</strong></td>
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<td>64.8(4.8)</td>
<td>100</td>
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<td>100</td>
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<td><strong>Relative end-diastolic volume (%)</strong></td>
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<td>100</td>
<td>134.4(9.5)</td>
<td>100</td>
</tr>
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<td><strong>Relative end-systolic volume (%)</strong></td>
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<td>100</td>
<td>151.9(16.2)</td>
<td>100</td>
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<td></td>
<td>2</td>
<td>151.9(16.2)</td>
<td>100</td>
<td>151.9(16.2)</td>
<td>100</td>
</tr>
<tr>
<td><strong>Mean ejection time (ms)</strong></td>
<td>1</td>
<td>179.4(7.8)</td>
<td>100</td>
<td>179.4(7.8)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>170.8(19.6)</td>
<td>100</td>
<td>170.8(19.6)</td>
<td>100</td>
</tr>
<tr>
<td><strong>Peak rate of change of volume (dV/dt)</strong></td>
<td>1</td>
<td>3.37(0.53)</td>
<td>100</td>
<td>3.37(0.53)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.63(0.27)</td>
<td>100</td>
<td>3.63(0.27)</td>
<td>100</td>
</tr>
<tr>
<td><strong>(end-diastolic vol s⁻¹)</strong></td>
<td>1</td>
<td>3.06 (0.11)</td>
<td>100</td>
<td>3.06 (0.11)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.91 (0.13)</td>
<td>100</td>
<td>2.91 (0.13)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.05 mg/kg felodipine</td>
<td>0.05 + 1 mg/kg felodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>-----------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 min</td>
<td>60 min</td>
<td>210 m</td>
<td>240 m</td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>76±13</td>
<td>85±16</td>
<td>85±16</td>
<td>78±14</td>
<td>85±18</td>
</tr>
<tr>
<td>B</td>
<td>51±3</td>
<td>58±5</td>
<td>58±5</td>
<td>53±5</td>
<td>59±4</td>
</tr>
<tr>
<td><strong>BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>160/95±13/11</td>
<td>126/77±12/9</td>
<td>126/76±18/11</td>
<td>139/85±24/12</td>
<td>113/69±19/10</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>0.51±0.06</td>
<td>0.58±0.06</td>
<td>0.59±0.07</td>
<td>0.52±0.08</td>
<td>0.58±0.06</td>
</tr>
<tr>
<td>B</td>
<td>0.52±0.09</td>
<td>0.59±0.09</td>
<td>0.58±0.07</td>
<td>0.57±0.06</td>
<td>0.62±0.08</td>
</tr>
<tr>
<td><strong>Δ CO(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>100</td>
<td>129±16</td>
<td>127±16</td>
<td>102±8</td>
<td>133±13</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>143±32</td>
<td>155±39</td>
<td>131±21</td>
<td>158±30</td>
</tr>
<tr>
<td><strong>Δ SV(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>100</td>
<td>111±17</td>
<td>112±13</td>
<td>108±13</td>
<td>114±12</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>124±21</td>
<td>131±27</td>
<td>123±18</td>
<td>134±19</td>
</tr>
<tr>
<td><strong>Δ SVR(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>100</td>
<td>62±14</td>
<td>63±10</td>
<td>73±18</td>
<td>55±6</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>60±19</td>
<td>57±18</td>
<td>72±17</td>
<td>48±10</td>
</tr>
<tr>
<td><strong>Δ PVV(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>100</td>
<td>104±7</td>
<td>102±10</td>
<td>100</td>
<td>94±3</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>102±3</td>
<td>101±4</td>
<td>100</td>
<td>103±4</td>
</tr>
</tbody>
</table>
TABLE 19

BLOOD PRESSURE, HEART RATE, WEIGHT AND ANKLE CIRCUMFERENCE AFTER 3 OR 6 WEEKS OF MINOXIDIL AND FELODIPINE BASED ANTIHYPERTENSIVE REGIME IN SEVERE HYPERTENSION

<table>
<thead>
<tr>
<th></th>
<th>Minoxidil</th>
<th></th>
<th>Felodipine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 week</td>
<td>6 week</td>
<td>3 week</td>
<td>6 week</td>
</tr>
<tr>
<td>Supine BP (mmHg)</td>
<td>155/89 ± 25/7</td>
<td>148/87 ± 23/11</td>
<td>149/87 ± 24/11</td>
<td>150/88 ± 19/8</td>
</tr>
<tr>
<td>Erect BP (mmHg)</td>
<td>146/89 ± 24/9</td>
<td>142/87 ± 22/11</td>
<td>137/85 ± 22/13</td>
<td>136/86 ± 14/10</td>
</tr>
<tr>
<td>Supine HR (bpm)</td>
<td>67.6 ± 13.6</td>
<td>68.9 ± 10.8</td>
<td>62.9 ± 12.7*</td>
<td>62.9 ± 7.1*</td>
</tr>
<tr>
<td>Erect HR (bpm)</td>
<td>69.6 ± 14.6</td>
<td>71.2 ± 9.9</td>
<td>68.0 ± 15.8</td>
<td>68.1 ± 10.1*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2 ± 13.0</td>
<td>81.4 ± 13.3</td>
<td>79.4 ± 13.5**</td>
<td>79.9 ± 13.1**</td>
</tr>
<tr>
<td>Ankle circumference cm</td>
<td>21.9 ± 1.5</td>
<td>22.1 ± 1.6</td>
<td>22.1 ± 1.7</td>
<td>22.1 ± 1.7</td>
</tr>
</tbody>
</table>

n = 15;  * p < 0.05;  ** p < 0.01
<table>
<thead>
<tr>
<th>Biochemical Data</th>
<th>Minoxidil</th>
<th>Felodipine</th>
<th>Laboratory Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (umol/l)</td>
<td>116.3 ± 31.78</td>
<td>116.5 ± 30.15</td>
<td>55 - 150</td>
</tr>
<tr>
<td>Random blood glucose (mmol/l)</td>
<td>5.6 ± 1.15</td>
<td>5.6 ± 1.80</td>
<td>3.6 - 11</td>
</tr>
<tr>
<td>Plasma potassium (mmol/l)</td>
<td>3.9 ± 0.31</td>
<td>3.8 ± 0.29</td>
<td>3.3 - 4.7</td>
</tr>
<tr>
<td>Plasma bilirubin (umol/l)</td>
<td>9.7 ± 2.44</td>
<td>10.0 ± 3.61</td>
<td>2 - 17</td>
</tr>
<tr>
<td>Plasma ALT (iu/l)</td>
<td>24.7 ± 13.28</td>
<td>28.9 ± 16.40</td>
<td>10 - 40</td>
</tr>
<tr>
<td>Plasma AST (iu/l)</td>
<td>23.7 ± 7.11</td>
<td>24.3 ± 9.22</td>
<td>10 - 35</td>
</tr>
<tr>
<td>Plasma alkaline phosphatase (iu/l)</td>
<td>86.6 ± 23.61</td>
<td>101.8 ± 29.23*</td>
<td>40 - 100</td>
</tr>
<tr>
<td>Plasma gamma glutamyl transpeptidase (iu/l)</td>
<td>24.3 ± 10.71</td>
<td>42.3 ± 31.44*</td>
<td>10 - 55</td>
</tr>
</tbody>
</table>

n = 15; * p < 0.01
APPENDIX
APPENDIX I

The work for this dissertation was carried out in the Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh under the supervision of Dr A L Muir, Reader, Department of Medicine and the work was performed by myself. Dr W J Hannan, Lecturer in Medical Physics and Engineering was the second observer in the studies of reproducibility. Dr W MacNee, Senior Registrar, collaborated with me in the acute study into the effect of pirbuterol.

My appointment during the time of preparation of this thesis has been Clinical Lecturer in General Medicine, Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh.
APPENDIX II

Part of this work has appeared in published form:


ACKNOWLEDGMENTS
I am indebted to Dr A L Muir, Reader in the Department of Medicine whose advice, encouragement and helpful criticism have been of great value. My thanks also to Professor M F Oliver, Professor J S Robson, Dr A C Douglas and Dr B F Clarke of the Departments of Cardiology and Medicine for allowing their patients to be included in the studies. I should like to express my particular thanks to Dr W J Hannan and Dr A Millar of the Department of Medical Physics and Dr C Adie and Dr H Brash of the Department of Medicine for their developmental work on the radionuclide methodology and help with the gamma camera computer system. Dr W J Hannan also helped me with the validation of these methods and I am particularly indebted to him.

Thanks are also due to Astra Pharmaceuticals for permitting the use of prenalterol and felodipine which they developed and I am most grateful to Dr R Goodfellow, Dr T W K Hill and Mrs E Forret for their cooperation. Thanks also to Pfizer Pharmaceuticals for supplying pirbuterol.

In addition I should like to thank Dr C McIntyre and Dr R Elton from the Department of Medical Computing and Statistics for their statistical advice and Miss S Turnbull and Miss F Taddei for excellent technical assistance; also Sisters B McLay and M Castle for nursing care.

Finally I should like to acknowledge my gratitude to the members of the Department of Medical Illustration and Mrs J Johnstone for painstakingly typing the manuscript.
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