ECHOCARDIOGRAPHIC STUDIES OF THE LEFT VENTRICLE IN PATIENTS WITH CHRONIC RENAL FAILURE

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Faculty of Medicine, for the degree of Doctor of Medicine by

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

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DECLARATION

The work in this thesis was carried out solely by Ellon McGregor and has not been published.

SUMMARY

With the greater availabilty and success of dialysis and renal transplantation programmes, cardiovascular disease has emerged as the dominant threat to survival of patients with end-stage renal failure. The identification of left ventricular hypertrophy as an independent determinant of outcome in such patients prompted this investigation into factors which might influence left ventricular mass. Reports of regresson of ventricular hypertrophy after renal transplantation suggested correction of uraemia, anaemia or hyperparathyroidism, either alone or in combination might be important.

The aim of this thesis therefore was to examine the left ventricle by means of established echocardiographic techniques in dialysis patients in relation to different therapeutic interventions. Patients were studied before and after renal transplantation, treatment with recombinant human erythropoietin for anaemia, and surgical parathyroidectomy for hyperparathyroidism. Stable dialysis patients were also studied at intervals.

Three hundred and seventy eight echocardiograms in 223 patients were performed and analysed by the author. A cross-sectional study of echocardiograms from dialysis patients revealed that men had greater left ventricular mass indices (LVMI) than women, after adjusting for body surface area. LVMI tended to increase with age, and was greatest in diseases associated with severe hypertension. Serial changes in LVMI followed no predictable pattern but correlated with changes in systolic blood pressure and haemoglobin. There were no differences between CAPD and haemodialysis subjects.

Following renal transplantation, the expected decrease in LVMI was not observed. However LV dimensions did change in most patients.

A search for factors which might be associated with these changes revealed that the most anaemic patients at the time of surgery had a greater reduction in end-diastolic dimension (EDD), while those with functioning arteriovenous fistulae had persisting elevation of EDD. Using multiple logistic regression analysis, systolic blood pressure and male sex were related to the pre-operative LVMI. Age at the start of dialysis treatment was the only covariate to be associated with outcome.

Successful treatment of renal anaemia with erythropoietin was associated with a small reduction in LVMI and LV wall thickness. Parathyroidectomy in dialysis patients resulted in similar changes.

Variability in response was a consistent feature in all of the study groups and led to further investigation of the influence of volume overload by assessing ventricular changes as a result of dialysis with fluid removal. Highly significant changes in all left ventricular diastolic dimensions were observed, indicating that the widely used method of determining LV mass is not suitable for serial assessment of dialysis patients who are subject to changes in fluid balance.

Chapter 1

CARDIOVASCULAR MORTALITY IN CHRONIC RENAL DISEASE

"The enlarged state of the heart would seem to bespeak some cause of obstruction to the circulation through the system beyond what we discovered". [Richard Bright, 1827 (1)].

An association between renal impairment and cardiac disease has been recognised since Bright described the post-mortem findings in twenty-five patients dying with nephrotic syndrome, seven of whom had enlargement of the heart. However, only with the introduction of effective renal replacement therapy (RRT), has cardiovascular disease emerged as the dominant threat to survival in end-stage renal failure (ESRF).

Section 1
Cardiovascular mortality and chronic renal disease - population data

A decline in the number of deaths from renal disease has been accompanied by an increase in deaths from cardiac disease in the general population over the past eight decades (2). This in part might be explained by the development, greater availability and success of techniques of dialysis and renal transplantation, without which people with ESRF could not survive. Nevertheless premature death among patients receiving RRT is unexpectedly common and data from the Registry of the European Dialysis and Transplant Association (EDTA), confirm that cardiovascular disease accounts for over half of these deaths (3).

The principal "cardiovascular" causes of death described by the EDTA during the last two decades are myocardial infarction, cardiac failure, cardiac arrest and cerebrovascular accident (Figure 1). As in the general population, coronary heart disease is reported more frequently in males, and in northern European countries (4,5) (Figure 2), although the relative risk of death from myocardial infarction (MI) in dialysis and transplant patients is far greater. In the United Kingdom, this relative risk in patients receiving renal replacement has been estimated to be at least five times higher than in age and sex matched subjects from the general population and in younger patients with end-stage renal disease (ESRD) the risk is almost ninety-fold. Overall the death rate in ESRF is equivalent to rates observed in patients with a history of a previous MI (5).

The underlying cause of renal failure also determines susceptibility to a cardiovascular event: with diabetes and renovascular hypertension the risk of MI and cerebrovascular accident is greater, than if glomerulonephritis is the primary renal disease (3). Furthermore the distribution of cardiovascular causes of death differs according to the type of renal replacement therapy (figure 3): following renal transplantation cardiac failure and cerebrovascular accidents are less frequently reported, while MI is observed as often in spite of transplanted patients tending to be fitter before acceptance for such surgery (6). Cardiovascular mortality is highest in the first year of treatment, be it transplantation or dialysis (7,8). In dialysis patients, the proportions of deaths from specific cardiovascular causes do not vary significantly with the method of dialysis employed (figure 3).

Although these data are incomplete (in 1989, 79% of centres in Europe submitted figures to EDTA) and the accuracy of diagnoses and death certification might be questioned, cardiovascular disease in patients with renal failure is a major problem in all countries offering renal

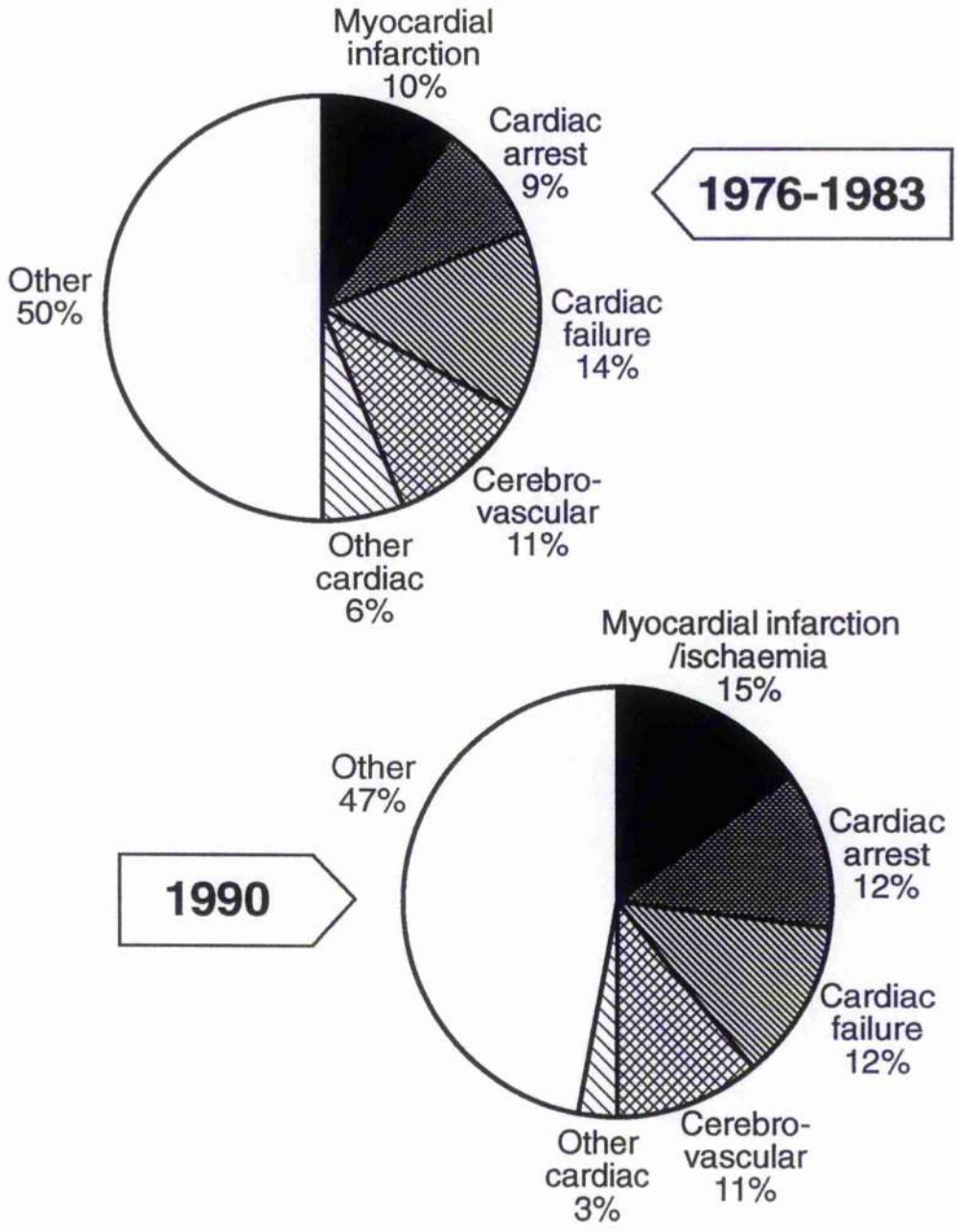

Figure 1

Cardiovascular causes of death on RRT in Europe, comparing 1976 -1983 with 1990 (from EDTA, references 3 and 5)

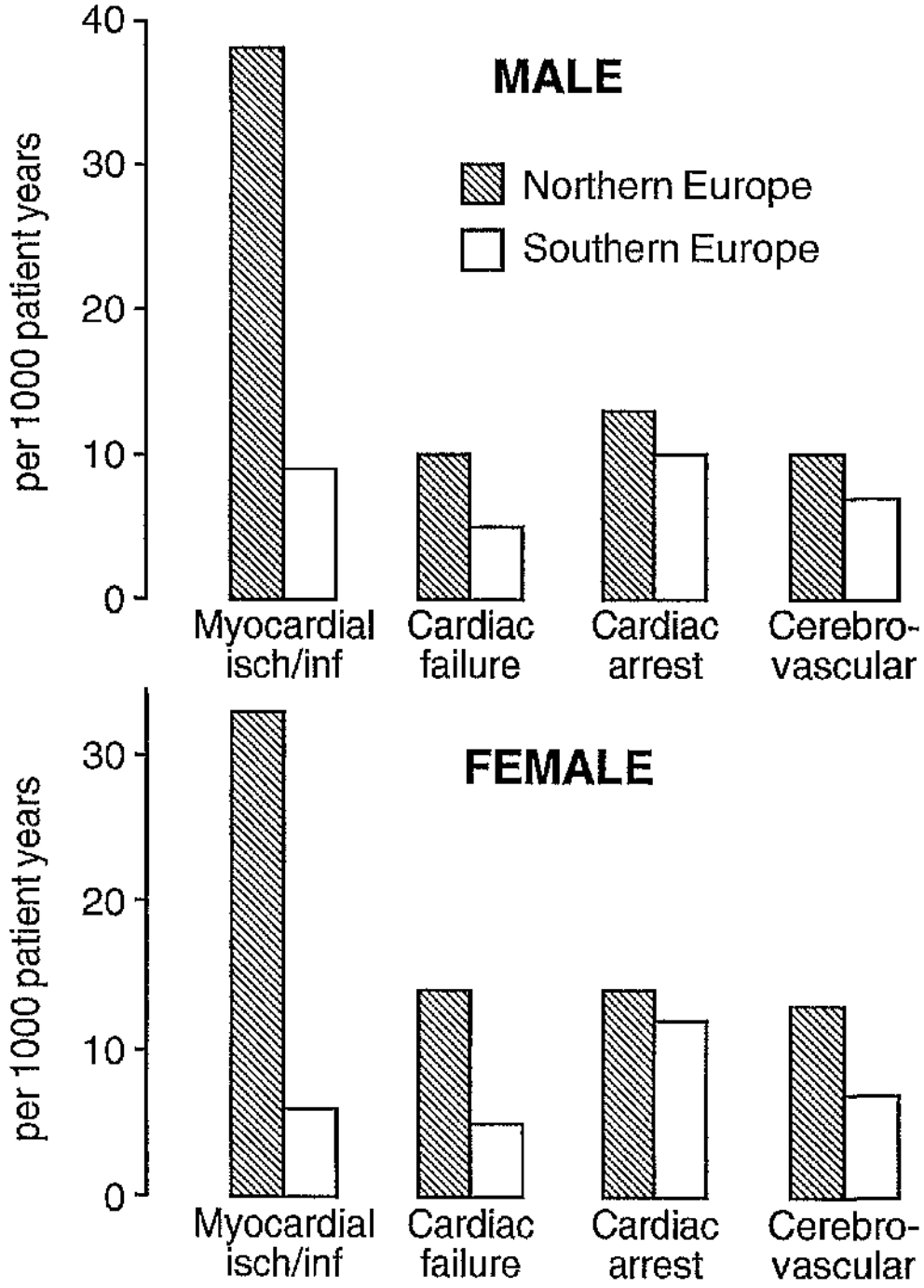

Figure 2

Death rates from all cardiovascular causes of patients aged 35-64 years, commencing RRT with all primary renal diseases (from reference 5)

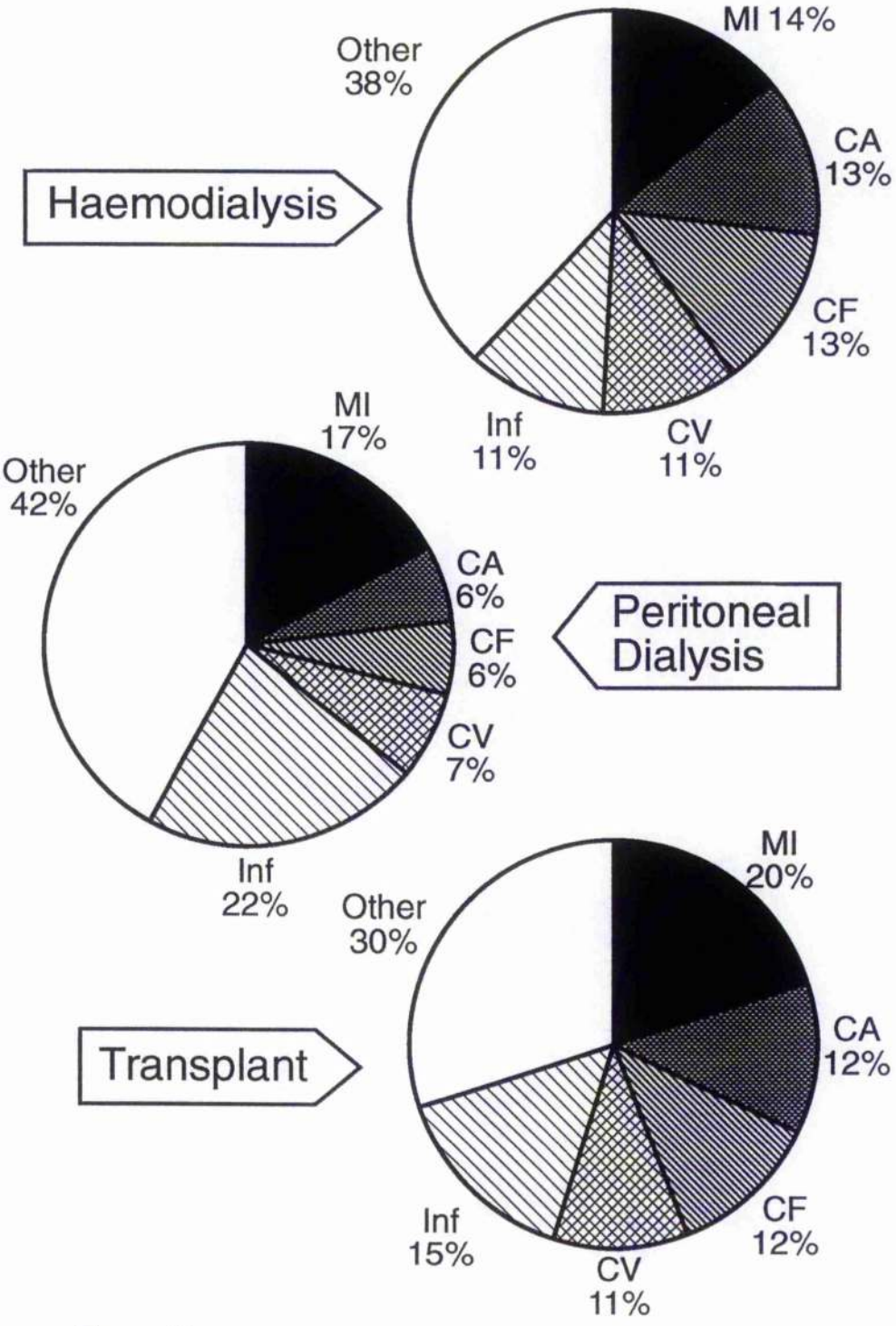

Figure 3

Cardiovascular causes of death in RRT patients in 1990 as a percentage of total deaths (from reference 5)

support (9) and shows no sign of abating (10). The reasons the loss from cardiovascular disease is so great are still disputed. Some authors claim that atherosclerosis is accelerated by prolonged haemodialysis treatment (11), while others explain the high mortality by an observed excess of the accepted cardiovascular risk factors (12,13,14).

Section 2

Cardiovascular risk factors and renal disease

Advanced renal impairment is invariably complicated by disturbances of electrolyte, fluid, endocrine and metabolic balance which lead in turn to volume overload, hypertension, anaemia, and hyperlipidaemia. Moreover, the primary renal disease, dietary and drug therapy, the method of renal replacement and altered lifestyle may further disrupt normal homeostasis. As a result, risk factors known to predispose to cardiac mortality, are frequently present in patients with ESRF, and additional risks conferred by uraemia or its treatment have been proposed (Table 1).

CARDIOVASCULAR RISK FACTORS	
Accepted	**Proposed**
age	
sex	anaemia
hypertension	arteriovenous fistula
hyperlipidaemia	hyperparathyroidism
cigarette smoking	nicotine retention
glucose intolerance	acetate dialysis
ventricular hypertrophy	transplant rejection
	malnutrition

Table 1 Cardiovascular risk factors in ESRD

The cardiovascular risk factors listed can be described as "vascular" - those which promote atherogenesis, or "ventricular" - factors affecting ventricular size or function. Some, are associated with both vascular and ventricular disease. The vascular risks in ESRD will be described briefly (sections 1.3 - 1.6) and left ventricular influences discussed in greater detail in Chapters 2, 3 and 4.

Section 3

Cigarette smoking and vascular disease in ESRF

Habitual tobacco consumption is common among patients with chronic illness (15), and in men receiving haemodialysis has been associated with an increased incidence of fatal MI and stroke (16). Hypertensive smokers on haemodialysis have a particularly poor prognosis and it has been suggested that exaggerated nicotine retention may predispose to cardiovascular disease (17). Smoking is also independently correlated with the development of cardiovascular complications after renal transplantation, although one group suggests the risk attributable to cigarettes is small (18).

Section 4

Hyperlipidaemia and vascular disease in ESRF

Another factor contributing to premature cardiovascular mortality is hyperlipidaemia, prevalent in both chronic and end-stage renal failure. It has long been considered part of the nephrotic syndrome, though the pathophysiology is still incompletely understood (19). Elevated cholesterol, low-density lipoprotein (LDL) and apoprotein B

concentrations, together with reduced levels of protective high-density lipoprotein (HDL) might suggest increased cardiovascular risk, but evidence for this is contradictory (20,21): heavy proteinuria however would seem to be associated with a higher than expected incidence of coronary heart disease (22).

Abnormal lipid metabolism has also been found in non-nephrotic renal disorders. As renal function deteriorates various lipase activities become impaired, resulting in defective triglyceride clearance and further exacerbated by a degree of insulin resistance (23,24). In addition HDL levels tend to fall while reduced receptor affinity for uraemic LDL results in higher circulating concentrations (25). In spite of these changes total cholesterol levels are often normal but lipoprotein composition altered, in such a way that catabolism yields atherogenic remnants (26).

A similar pattern of hypertriglyceridaemia with normal or low cholesterol has been described in patients treated by maintenance haemodialysis or CAPD (27). After dialysis patients undergo renal transplantation, their lipid profiles change, but usually remain abnormal: hypertriglyceridaemia improves though persists in twenty percent, while cholesterol fractions rise (28). In contrast to experience in large hyperlipidaemic populations (29,30), there is no evidence that use of lipid-lowering drugs in renal patients will reduce the incidence of MI.

Section 5
Glucose intolerance and vascular disease in ESRF

Over 10% of new patients now accepted for "long term" renal replacement therapy (RRT) in Europe are diabetic, and therefore at increased risk of developing cardiovascular disease (31). The three year survival of 25 to 35 year olds with diabetic nephropathy starting dialysis

but not transplanted is only 60%, compared to 85% in all similarly aged RRT patients (4). Although the mortality from MI is greater in diabetic patients (5), the majority of deaths are sudden, of unknown cause, and notably often associated with cardiomegaly (32).

Transplanted diabetic patients also have a poor prognosis: in a study of 100 insulin dependent diabetics with ESRF undergoing pre-transplant assessment, 37 had significant cardiac disease (advanced coronary occlusive disease and/or significant left ventricular dysfunction) (33). Fifty-eight were later transplanted and among those with pre-existing double or triple coronary vessel disease, mortality was high. Less severe coronary artery narrowing was also shown to progress after renal transplantation. The importance of pre-operative vascular disease in relation to prognosis after renal transplantation has been substantiated (34,35) and now full pre-operative cardiac investigation is advocated. The death rate from myocardial infarction and ischaemia in transplanted diabetic patients consistently exceeds the rate in non-diabetic transplant recipients (5), but is disproportionately high in the first week (31).

How might "at risk" diabetic patients be identified? The duration of diabetes before ESRF is inversely correlated to survival thereafter (36), but there are few pointers. The absence of coronary artery narrowing on coronary arteriography is not necessarily reassuring as disease of small vessels may lead to the development of a "diabetic cardiomyopathy" and premature death (37,38). However among dialysis patients, there is no evidence that diabetics have an excessive degree of systolic myocardial dysfunction, compared with non-diabetics (39). On the other hand, diastolic ventricular compliance may be impaired in diabetics with proteinuria, perhaps reflecting early hypertensive heart disease (40).

Section 6

Hypertension and vascular disease in ESRF

As the glomerular filtration rate falls, the prevalence of hypertension increases and reaches eighty percent in patients with ESRD (41,42). Patients with hypertension secondary to renal parenchymal disease have a significantly higher cardiovascular mortality even before they reach end-stage renal failure, than men and women with hypertension resulting from other causes (43). Those with renovascular disease are also recognised to be at increased risk (3). Ischaemic heart disease is the leading cause of death to account for this high age-adjusted mortality in hypertensive patients with underlying renal disease, many of whom have high blood pressures despite treatment, and electrocardiographic (ECG) abnormalities. In a study which examined the degree of atherosclerosis in the iliac vessels of fifty haemodialysis patients about to undergo renal transplantation, age and hypertension were related to moderate and severe vascular disease, and without exception, all young patients with diseased vessels had been hypertensive (44).

Mortality is especially high in hypertensive patients with ECG evidence of left ventricular hypertrophy or previous MI (45). Moreover data from the Framingham study suggest that the risk associated with electrocardiographic left ventricular hypertrophy is greater than the risk attributable to hypertension alone (46). Thus, it is now clear that the high death rate among hypertensive patients cannot be explained solely by vascular disease. Left ventricular hypertrophy is an additional risk factor for cardiac mortality in hypertension, and indeed is a stronger predictor of hypertensive complications than blood presure itself (47).

Cardiac hypertrophy was not perceived as posing special risk to patients already suffering the multiple problems of chronic renal failure, until Silberberg published his important study showing left ventricular hypertrophy to be an independent determinant of survival in patients with end-stage renal disease (48).

Chapter 2

RISKS ASSOCIATED WITH LEFT VENTRICULAR HYPERTROPHY

Before considering the heart in chronic renal disease, the prevalence, pathogenesis and prognosis of left ventricular hypertrophy in general will be reviewed.

Section 1

Left ventricular hypertrophy in the general population

Reports from the Framingham Study first indicated that abnormalities of the electrocardiogram suggestive of left ventricular hypertrophy are associated with an increased risk of fatal coronary heart disease (49) and sudden death (50) in the general population. However, electrocardiographic changes may be absent in genuine cases of cardiac hypertrophy, irrespective of the criteria employed, and echocardiography is undoubtedly a more sensitive method for detecting increased left ventricular mass (51,52).

Subsequent echocardiographic studies from Framingham have pointed to a prevalence of left ventricular hypertrophy of 16% in men and 19% in women (53), in contrast to previous electrocardiographic estimates of 3.2% (46).

The earlier observations linking left ventricular hypertrophy to an increased incidence of cardiovascular events have not only been confirmed, but elaborated: in middle-aged and elderly men and women left ventricular hypertrophy is associated with cardiovascular disease, death from cardiovascular disease and death from all causes (54). The greater the left ventricular mass, the greater is the risk of non-fatal and

fatal cardiac events, and the relationship persists after adjusting for age, diastolic blood pressure, smoking, obesity, diabetes and other variables. Left ventricular hypertrophy has therefore become established as an independent cardiovascular risk factor.

Section 2

The development of left ventricular hypertrophy

Embryonic development of the human myocardium, involves hyperplasia (growth through cell division) of undifferentiated myogenic cells, which later acquire the ability to synthesise myofibrillar proteins (55). Studies in the chick embryo, reveal continuing mitosis throughout fetal life with accumulation and longitudinal alignment of myofibrils until characteristic spindle shaped myocytes become recognisable (56).

After birth, mitotic activity in myocytes ceases, though myocardial connective tissue cells retain the capacity to divide (55). Normal postnatal cardiac development is therefore dependent on myocyte hypertrophy (growth through cell enlargement) and non-muscle cell hyperplasia (57). Increased collagen and fibrosis have also been observed in cases of "pathological" cardiac hypertrophy (58,59,60), and in extreme hypertrophy, division of ventricular muscle cells and their nuclei may occur (58). Although the mechanism of such cleavage is poorly understood, it is likely to represent splitting rather than DNA replication (61).

Left ventricular size is governed by the work undertaken, namely the generation of sufficient pressure within the ventricular cavity to expel blood. With a thin-walled sphere, Laplace has determined that the wall stress or tension (T) is related to the radius (R) of the sphere and to the pressure (P) within

$$T = P \times R/2$$

or $$P = T \times 2/R$$

Because the left ventricle is a "truncated ellipsoid"(62), rather than a sphere, the amount of tension (T) that must be created at any one point to produce a given pressure (P) is expressed as

$$P = T (1/R_1 + 1/R_2)$$

where R_1 and R_2 are the principal radii of the curvature at that point.

This expression assumes R_1 and R_2 are large compared to ventricular wall thickness, but if the wall is thickened, the forces within it will not be evenly distributed. There is however evidence that tension is directly related to wall thickness (WT) (though the precise mathematical relationship is uncertain) (63).

$$P \alpha T (WT/R_1 + WT/R_2)$$

Thus, if the pressure increases and the left ventricular internal radii remain constant, wall thickness must increase to maintain wall tension. Conversely, if the pressure remains constant, but the ventricle dilates, an increase in wall thickness would also serve to sustain tension. Indeed, it has been suggested that the main purpose of cardiac hypertrophy is to preserve wall tension within normal limits (64).

Work (W) done by the heart, can be calculated from a derivation of the formula

$$W = F \times d$$

F - force
d - distance

In the circulatory system, pressure (P) is analogous to force per unit area (a)

$$P = F/a$$

$$W = P \times a \times d$$

$$a \times d = V \qquad V \text{ - volume}$$

$$W = P \times V$$

As ventricular pressure varies during ejection, the work done is expressed more accurately as

$$W = \int P \, dV$$

Since systolic aortic pressure closely approximates the integrated ventricular systolic curve, the stroke work (SW) of the ventricle is equal to the product of the mean systolic aortic pressure (MAP) and the stroke volume (SV).

$$W = MAP \times SV$$

Both increased pressure and increased stroke volume (from ventricular dilatation) will therefore add to cardiac work load, which will in turn promote cardiac hypertrophy (65).

Section 3

Hypertrophy - pressure versus volume overload

The type of stress imposed upon the left ventricle determines the pattern of hypertrophy (66). When systolic pressure is raised, as a result of hypertension or aortic outflow obstruction, the left ventricular wall becomes uniformly thickened and chamber size remains unchanged - concentric hypertrophy (65). This effect is achieved through an initial though not sustained period of dilatation (67), a prompt increase in efficient myocardial protein synthesis (68,69), and possibly addition of new myofilaments leading to myofibrillar growth and even splitting (70).

As a consequence, the pressure load is distributed over a larger number of contractile elements and the force per unit area remains constant.

In contrast, when the left ventricle is distended abnormally, as in chronic anaemia, arteriovenous shunting or states of fluid overload, the diastolic intraventricular volume increases. To maintain ventricular wall thickness, the muscle mass must also increase. Under such conditions of volume overload, the pattern of hypertrophy is uniform, but described as eccentric, because the heart is displaced to the left of the chest on x-ray. (64,66).

Chronic ventricular dilatation is associated with early enhanced myocardial protein synthesis (68,71), and in the model of the volume overloaded dog, progressive recruitment but not over-stretching of sarcomeres (72). This poses the question - how does the chronically dilated left ventricle expel an augmented stroke volume if not by a Frank-Starling response at sarcomere level? Although this mechanism may be important acutely, in chronic models, the generation of more sarcomeres permits normal performance over a greater circumference, in spite of the mechanical disadvantage conferred by dilatation.

Section 4

Determinants of left ventricular mass

Framingham data have pointed to a high prevalence of left ventricular hypertrophy in the community (53). With almost one fifth of the study population of 4976 participants affected, it was possible to undertake multivariate analyses to identify independent risk factors for left ventricular hypertrophy. Evidence from other population studies is also considered.

2.4.1 Hypertension

The prevalence of left ventricular hypertrophy in hypertensive patients has been variously reported at 23 to 48% compared with a prevalence of 0 to 10% in normal subjects (73,74,75). Among employed patients with uncomplicated essential hypertension, the prevalence of hypertrophy was 12% in workers with borderline elevation of blood pressure (SBP 140-159 or DBP 90-94) and 20% in a group with more severe hypertension (SBP>160 and/or DBP>95) (76). This would suggest that the higher the blood pressure the greater the risk of left ventricular hypertrophy and early work supported such an hypothesis (77,78). Later studies then questioned the rather weak correlation between blood pressure and ventricular mass, particularly if blood pressure was measured by a doctor (75,79). When ambulatory blood pressure is monitored continuously, a significant relationship between left ventricular mass index and blood pressure (systolic or diastolic) may become apparent (80), but in one study this relationship held only in patients with normal ventricular mass (81). Variabilty of frequent blood pressure measurements might also be a predictor of left ventricular hypertrophy in patients treated for essential hypertension (82), but overall the correlation between blood pressure, however measured, and left ventricular mass is poor, suggesting factors other than blood pressure are important in the pathogenesis of cardiac hypertrophy.

Recently the conventional view that increased afterload from hypertension leads to cardiac hypertrophy has been challenged (83). Devereux has considered a growing body of evidence which shows that left ventricular hypertrophy may preceed and indeed predict high blood pressure and has suggested that increased muscle mass might be the primary abnormality responsible for exaggerated pressor responses (84).

Without longitudinal studies which start in childhood and monitor blood pressure and left ventricular mass, this issue cannot be resolved.

2.4.2 Age

A positive correlation between left ventricular wall thickness and age has been demonstrated in men without hypertension or overt cardiovascular disease (85), and large population studies have consistently identified age as an independent determinant of cardiac size (53,76,86). Whether subtle and unrecognised changes in blood pressure explain these observations or whether they reflect reduced vascular compliance and hence increased peripheral vascular resistance is uncertain.

A syndrome of severe concentric cardiac hypertrophy in elderly, hypertensive, and often black patients has also been described (87). In this condition, named "hypertrophic cardiomyopathy of the elderly", the degree of hypertrophy exceeds expectation, given the level of blood pressure or evidence of other end-organ injury. Diastolic function is impaired and vasodilator drugs, prescribed because of heart failure at time of presentation, are tolerated poorly. The relative importance of age, hypertension and race in predisposing to this syndrome have not been defined.

2.4.3 Race

Several studies have suggested that black hypertensive patients matched for age, sex and arterial blood pressure, may have a higher prevalence of left ventricular hypertrophy than white patients (76,88,89). However the findings must be interpreted cautiously because they rely on

the use of derived indices for muscle mass, whereas absolute measurements of wall thicknesses are no different between racial groups. Failure to take into account determinants of cardiac size other than simply age and arterial pressure could lead to spurious conclusions.

2.4.4 Body mass

It is recommended that echocardiographic measurements of left ventricular mass should be standardised by relating mass (g) to body size, preferably body surface area (g/m^2) (90,91). Even with such correction, obesity in mildly hypertensive patients may be more important than blood pressure in determining cardiac size (92). Similarly, relative weight, as assessed by insurance companies, has also been shown to correlate better with left ventricular mass than does blood pressure (93). This might reflect the effects of increased cardiac output and augmented stroke volume on the left ventricle (94).

2.4.5 Exercise

Physical exertion imposes demands upon the heart, either in the form of pressure overload or volume overload. Pressure overload results from isometric exercise, such as weight-training, during which extreme rises in blood pressure can develop. Just as hypertension can cause concentric left ventricular hypertrophy (65), isometric exercise can produce considerable wall thickening (95), though this should be related to the accompanying increase in lean body mass.

Isotonic exercise or endurance training leads to periods of sustained increase in cardiac output (96). As might be expected, the left ventricular cavity expands (95), and ventricular wall thickness increases

(97). Athletes, irrespective of the nature of their activity, manifest a number of rhythm disturbances more frequently than expected (98), of which a resting bradycardia is most common. Because the cardiac output in isotonic athletes at rest is normal, stroke volume must increase with training (99).

The long term effects of exercise-induced cardiac adaptation are not proven, but it has been suggested athletes may be at incresed risk of sudden death, particularly if performance enhancing drugs such as erythropoietin have been used (100).

2.4.6 Blood viscosity

It is recognised that haematocrit and whole blood viscosity are higher in hypertensive patients (101), and that even minimal elevation of blood pressure is associated with increased blood viscosity (102). Another factor also related to hyperviscosity, is cigarette smoking (103). Thus, the higher rates of cardiovascular morbidity and mortality reported in syndromes causing polycythaemia might be indirectly attributed to an excess of these risk factors (104,105,106).

Equally, haematocrit or whole blood viscosity might be cardiovascular risk factors, though conclusive evidence for this is not available. However whole blood viscosity has been shown to be more closely related to left ventricular hypertrophy than either systolic or diastolic blood pressure in patients with essential hypertension (107). Whether this is because cardiac hypertrophy and increased viscosity are both the effects of a common stimulus, or whether elevated viscosity is directly responsible for cardiac growth is not known. Poiseuille's Law which relates vascular resistance directly to blood viscosity and indirectly to the fourth power of vessel radius indicates that an elevation in whole

blood viscosity will result in increased total peripheral resistance, which in turn promotes cardiac hypertrophy. Alternatively, vasoconstriction could be the primary abnormality and by inducing haemoconcentration cause a rise in blood viscosity. Under conditions of vasoconstriction, contraction of plasma volume is accompanied by an increase in peripheral resistance (108), which is an additional stimulus to left ventricular hypertrophy.

2.4.7 Anaemia

While a raised haematocrit may influence the left ventricle, so too may a low haematocrit. The impact of chronic anaemia on the heart has been studied in greatest detail in sickle cell disease. Affected patients have been found to have enlarged ventricular cavities in both systole and diastole, greater stroke volume, increased septal width and greater left ventricular mass (109,110). Hypertrophy may not be associated with overt left ventricular dysfunction (109,110). However when the effects of altered loading conditions on systolic function are considered, impaired contractility can be demonstrated (111).

The cardiac changes in sickle disease have been attributed to long standing volume overload, and bear similarity to cardiac adaptations to increased cardiac output in animals with arteriovenous fistulae (112) and pregnant women (113). Restoration of normal circulating volume by repeated blood transfusion in children with sickle cell anaemia (114), shunt reversal in laboratory dogs (112), or delivery of pregnant women (113), result in the return of cardiac chamber size to normal and reduction in left ventricular mass.

2.4.8 Sympathetic nervous system

Administration of exogenous catecholamines to experimental animals will induce hypertrophy of the myocardium (115), an effect sustained in the face of blood pressure control by alpha blockade (116). Furthermore, Yamori found that simultaneous beta adrenergic receptor blockade ameliorates the hypertrophic response to noradrenaline infusion (116). Later cell culture work challenged this evidence, by showing the increase in myocyte size to be an alpha adrenergic response (117). Nevertheless noradrenaline was seen to be "the myocardial hypertrophy hormone", capable of inducing myocardial cellular growth independently of changes in blood pressure (118).

Although findings in animal models may not apply to man, Dunn and Allen's observations on regression of left ventricular hypertrophy in hypertensive patients treated with beta blocking agents would indirectly support a role for the sympathetic nervous system in the pathogenesis of human cardiac hypertrophy (119,120).

2.4.9 Renin - angiotensin system

Angiotensin II infusion at a mildly pressor dose has been shown to produce an early increase in myocardial protein synthesis and ventricular weight (121). The advent of converting enzyme inhibitor drugs has therefore provided scope for further research in this area. Sen and colleagues (122) implicated the renin-angiotensin system in the pathogenesis of hypertrophy by reporting contrasting effects of antihypertensive agents on plasma and renal renin concentrations in relation to left ventricular mass: although minoxidil controlled blood pressure in spontaneously hypertensive rats, this was associated with

increased renin levels and ventricular weight remained constant. On the other hand, propranolol had less effect on blood pressure, but caused a fall in plasma renin and a reduction in left ventricular mass. With methyl dopa, a fall in both blood pressure and renin was accompanied by a decrease in cardiac mass. Further experiments by the same group in the same model, demonstrated that use of the converting enzyme inhibitor captopril (SQ 14225), prevented the development of hypertension and cardiac hypertrophy in young rats, and led to control of blood pressure and reversal of hypertrophy in older hypertensive rats (123).

In humans the potent hypotensive effects of converting enzyme inhibitors and beta adrenergic antagonists cannot be divorced from any possible direct action on the myocardium in attempting to explain the reduction in left ventricular mass that occurs with treatment (119,124).

2.4.10 Parathyroid hormone

An association between hypertension and hyperparathyroidism has long been recognised (125), but the relationship between cardiac hypertrophy and hyperparathyroidism was only first suggested when Symons et al. found elevated parathyroid hormone (PTH) levels in five of eighteen patients with hypertrophic cardiomyopathy and left ventricular hypertrophy in all but one of sixteen patients with primary hyperparathyroidism (126). As hypertrophy was not identified in patients with hypercalcaemia for other reasons (126), a PTH induced increase in transmembrane calcium flux, was the mechanism proposed (127).

This work, as well as reports of high levels of free intracellular calcium in patients with essential hypertension (128), stimulated Dominiczak and colleagues to study platelet free calcium in hyperparathyroidism, relating calcium levels to arterial blood pressure

and left ventricular mass (129). Although her subjects with primary hyperparathyroidism had both significantly elevated blood pressure (compared to controls) and hypercalcaemia, their intracellular free calcium levels were lower than expected, and several explanations were offered. Of special interest however, was that left ventricular mass index in the primary hyperparathyroid group was higher than in control subjects matched for age, sex and blood pressure and moreover fell slightly after parathyroidectomy, despite continuing high blood pressure. These findings support the view that parathyroid hormone has an effect on the left ventricle, at least in primary hyperparathyroidism.

2.4.11 Other endocrine disorders

Cardiac hypertrophy has also been described in phaeochromocytoma, acromegaly and hyperthyroidism (130). In the first two conditions, hypertension could be a contributing factor, and in hyperthyroidism, volume overload. In addition, catecholamines (115) and thyroxine (131) produce hypertrophy in experimental animals, and it is likely that specific hormonal effects are also important.

Section 5
Physiological or pathological hypertrophy?

The development of hypertrophy in response to haemodynamic loading of the left ventricle appears to be a useful physiological adaptation, as it enables the heart to undertake increased work without compromising function. However, pressure and volume overload are not uncommonly associated with cardiac failure, and it has been suggested

that cardiac hypertrophy facilitates normal function only when stresses are not sudden, severe or sustained (132,133).

Whether, or at which point, physiological hypertrophy becomes pathological on account of impaired function is difficult to determine, but aging and coronary vessel disease predispose. Diagnosing dysfunction in humans can be awkward because measures of systolic function are influenced by volume loading, and simple and reliable methods of assessing diastolic function are not available.

Nevertheless, Gaasch has evaluated use of the ratio of diastolic left ventricular radius to wall thickness, as a means of differentiating between physiological, or compensated hypertrophy on the one hand, and on the other, pathological, inadequate or inappropriate, hypertrophy (134).

Section 6
Effects of left ventricular hypertrophy

The increased morbidity and mortality associated with left ventricular hypertrophy can be attributed to angina pectoris, non-fatal and fatal myocardial infarction, congestive cardiac failure, and sudden death. From ante- and post-mortem studies of human hearts and experiments in animals, a number of mechanisms are thought to be responsible.

2.6.1 Myocardial ischaemia and hypertrophy

Volume or pressure loading of the left ventricle results in increased oxygen uptake and myocardial oxygen requirements are uniformly related to wall stress (135). Once hypertrophy is established, the greater oxygen requirements are maintained because of greater metabolic activity. In

part these demands can be met through increased oxygen extraction from capillary blood by the hypertrophied myocardium (136). In addition, blood flow may be augmented, as ventricular growth is accompanied by a significant proliferation of capillaries (137), though the overall density of capillaries is still diminished (138). Blood flow studies indicate that endocardial perfusion in hypertrophioed dog hearts is reduced in comparison with normal hearts and stress in the form of ischaemia induced vasodilatation further accentuates the regional hypoperfusion (139). The suspicion that this subendocardial area might be vulnerable to ischaemia is supported by the demonstration of subendocardial fibrosis in patients who died with hypertension (60) or aortic stenosis or coarctation (140). Indeed, the degree of scarring of the endocardium correlates directly with heart weight (141) and the intrinsically high oxygen consumption in this part of the heart may amplify susceptablity to hypoxic damage (142) and explain the non-uniform distribution of scar tissue.

Blood supply may be further compromised in the presence of coronary artery disease, which frequently coexists with left ventricular hypertrophy (143,144), perhaps because atherogenesis and hypertrophy share several pathogenetic factors. While myocardial infarction may result in compensatory hypertrophy, there is no evidence that left ventricular hypertrophy per se causes major coronary vessel disease. However significant narrowing of small intramyocardial arteries from intimal proliferation has been reported in hypertensive hearts (145). Such changes could explain the diminished coronary flow reserve described in patients who have cardiac hypertrophy and typical anginal pectoris, yet angiographically normal epicardial coronary arteries. (146).

2.6.2 Systolic function of the left ventricle

Early studies which described normal or enhanced myocardial contractility in animals (147), papillary muscle preparations (148), and humans with cardiac hypertrophy have been contradicted (149) and criticised on a number of points. First, it is important to relate tension to unit area of ventricular wall (150). Second, experimental techniques used to induce cardiac hypertrophy such as banding of the aorta or pulmonary artery can alter ventricular function by causing myocardial fibrosis (151) and third the timing of assessment of systolic function may affect results (152). In addition, alterations in both preload and afterload can influence widely used measures of systolic function, such as ejection fraction, fractional shortening and velocity of circumferential fibre shortening, independently of changes in muscle function. Left ventricular end-diastolic diameter is dependent on left ventricular end-diastolic pressure or preload, and end-systolic volume will be determined in part by end-systolic force or afterload. As a consequence, the value of accepted indices of contractility may be limited, at least in conditions of volume overload, valvular dysfunction or hypertension. However the end-systolic volume is not dependent on the initial ventricular volume (153) and the relationship between end-systolic length (or volume) and end-systolic force (or pressure) is linear (154). Therefore it has been suggested that the slope of the end-systolic afterload plotted against end-systolic volume will vary with contractile function rather than load and that the study of this relationship under varying loading conditions offers the most precise method of assessing muscle function (155,156,157). In states of cardiac hypertrophy, wall stress is preferred to pressure as a measure of afterload because it allows for left ventricular thickness (158). Studies of left ventricular fractional shortening and systolic wall stresses in

hypertrophied hearts have endorsed these findings and suggested that cardiac performance is initially maintained, but declines with progressive rise in afterload, particularly when ventricular dilatation is a feature (159,160).

2.6.3 Diastolic function of the left ventricle

Normal diastolic function implies complete filling of the left ventricle during diastole which depends on full relaxation of myocardial fibres and the elastic recoil of the ventricular wall. The "relaxation" is in fact an active process of calcium uptake by the sarcoplasmic reticulum and hydrolysis of ATP (161). Thereafter opening of the mitral valve facilitates diastolic filling of the left ventricle, the result of both the pressure gradient between the left atrial and ventricular chambers and the inherent passive elastic properties of the left ventricle. Only at rapid heart rates, does the atrial contraction contribute to diastolic filling in health.

Abnormal left ventricular diastolic function, in the presence of normal systolic function has been described in hypertensive patients (162), even before cardiac hypertrophy has developed and has been attributed to altered collagen composition within the myocardium impeding elasticity (163). Ischaemia may further compromise diastolic relaxation either by reducing the potential for oxidative phosphorylation (164) or causing fibrosis. Amyloid deposition in older hearts also impairs diastolic function.

In conditions of reduced diastolic compliance, atrial systole is important in maintaining ventricular filling. This has been demonstrated by doppler measurement of the peak early flow velocity through the mitral valve (E wave) and the maximal late flow velocity generated by atrial contraction (A wave) (165). In hypertrophied hearts with diastolic

dysfunction the ratio of E to A is reduced, although the index must be interpreted cautiously as transmitral flow may be influenced by haemodynamic loading (166,167). However, radionuclide ventriculography in the study of movement of technetium-labelled red cells has verified the prolongation of ventricular filling in hypertensive subjects (168).

2.6.4 Sudden death and left ventricular hypertrophy

In the Framingham Study sudden death was was first linked with left ventricular hypertrophy (46) and a later publication reported a five fold increase in people with electrocardiographic left ventricular hypertrophy (169). Post mortem studies have confirmed hypertrophy to be a common finding in such victims, although an excess of coronary artery disease does not appear to be present (170). McLenachan et al have demonstrated that complex ventricular arrhythmias occur more frequently in hypertensive patients if echocardiographic left ventricular hypertrophy is present and are not explained by poorer blood pressure control, cigarette consumption, diuretic therapy or hypokalaemia. (171). Arrhythmias are now widely believed to be responsible for sudden death in patients with cardiac hypertrophy.

Chapter 3

THE LEFT VENTRICLE IN CHRONIC RENAL FAILURE

While vascular disease accounts for considerable morbidity and mortality among patients with chronic renal failure, a growing body of evidence suggests that ventricular disease may also play an important and hitherto underestimated role.

Section 1

The heart and renal disease - in the past

After Richard Bright's early observations of cardiac hypertrophy in patients with nephritis, several of his contemporaries also documented the association (172). However, the nature of the relationship between cardiac and renal disease was not examined in detail until Saundby published his views on the role of hypertension later in the nineteeth century (173). In 1910, Oertel reiterated similar theories (174), then Evans, in a pathological study of arteriosclerosis in chronic renal disease, implicated raised blood pressure in the pathogenesis of both vascular lesions and ventricular hypertrophy. Evans also concluded that with few exceptions chronic renal disease caused cardiac hypertrophy, and was the commonest cause in patients under the age of thirty-five years without heart or lung disease (175). In both this and Solomon's post-mortem study of uraemic hearts (176), atheroma of the coronary arteries was a relatively infrequent finding and bore no relationship to heart weight.

Richter and O'Hare who had the opportunity to follow sixty-six patients with chronic glomerulonephritis in life, observed that cardiac symptoms rarely occured until the year preceeding death (177). The

majority of deaths resulted from uraemia and pericarditis was a common post-mortem finding in 48 percent, clinical signs having been present in most in the late pre-terminal phase. Half of the of patients who died of uraemia had increased heart weights, mainly due to the left ventricle, and even hearts of normal weights still exhibited left ventricular hypertrophy. The incidence of coronary artery disease in these patients equalled that reported in non-hypertensive heart disease, in spite of a history of hypertension in almost all.

As well as hypertrophy, Gouley described focal areas of myocardial degeneration in the hearts of patients suffering chronic glomerulonephritis and hypertension and suggested this might be the result of "uraemic intoxication" (178). Solomon also commented upon various microscopic cardiac lesions in other terminal renal diseases (176). These, he described as widespread areas of fatty degeneration and points of miliary myocardial necrosis, often associated with acute interstitial myocarditis. In his report of fifty patients, twenty-six had clinical cardiac failure, and twenty-five of these, focal lesions of the myocardial fibres. His conclusion however was that there was no specific cardiac lesion which could be considered characteristic of the uraemic state. Raab noted similar post-mortem appearances in uraemic hearts and from further animal experiments in which the cardiac effects of human uraemic sera were tested, deduced that catechol-like compounds were responsible for depressed cardiac function (179)

At that time any influence of left ventricular hypertrophy on the electrocardiogram was ignored, although characteristic features of hyperkalaemia (180) and repolarisation changes wbich would be compatible with left ventricular hypertrophy and strain pattern (179) were recognised. Much of the subsequent work which has added to the understanding of ventricular disease in renal failure stemmed from

studies in hypertension, because with the development of dialysis and transplantation, nephrological attention turned away from pathological review towards improving survival in uraemia by the "replacement" of renal function.

Section 2

The heart and renal disease - in the present

During the past thirty years both the potential and limitations of renal replacement therapy have been recognised. With dialysis and frequently transplantation, only "partial replacement" is achieved and perhaps this is one of the reasons why such high mortality rates in end-stage renal disease are observed. However identifying specific factors which explain the mortality and in particular the high incidence of cardiovascular complications in uraemia, has proved difficult. The widespread assumption that risks which predispose the general population to cardiovascular disease apply in renal failure is largely unsupported, but would seem reasonable.

From the few studies which have attempted to recognise predictors of survival in patients with end-stage renal disease at the start of their renal replacement therapy, age, duration of diabetes, left ventricular failure (181) and left ventricular hypertrophy (48) have emerged as definite risk factors. Symptoms of left heart failure appear to be more important than symptoms of ischaemic heart disease in determining outcome (181), and the influence of increased left ventricular mass persists when adjusted for age, coronary heart disease, diabetes and systolic blood pressure (48). As both the size and function of the left ventricle may have prognostic significance, the prevalence and pathophysiology of ventricular disease in uraemia deserve attention.

3.2.1 Cardiac morphology and function in chronic renal failure

Many of the pathologists' findings (Section 1) have been identified in patients with renal impairment, by means of non-invasive investigations. M-mode echocardiography has revealed the presence of pericardial effusions and thickening, left ventricular hypertrophy and dilatation, and valvular calcification and vegetations in symptomatic patients with chronic renal failure in the pre-dialysis period (182). It has also proven valuable in assessing ventricular function in such patients (183). However, more commonly studies have been undertaken in patients with end-stage renal failure after the start of dialysis when aortic, left atrial, valvular, and a spectrum of ventricular abnormalities may be present (184). As the techniques of echocardiography and radionuclide imaging have developed, knowledge of the structure and function of the left ventricle in uraemia has grown.

Numerous studies, employing various echocardiographic (184, 185,186,187,188,189,190,191,192,193,194,195,196,197,198,199, 200,201,202,203,204,205,206) and angiographic (207,208,209) methods have identified left ventricular hypertrophy in dialysis patients. Reports of its prevalence range between 42% (43) and 90% (39), depending upon the technique used, the method of determining left ventricular mass, and the criteria defining left ventricular hypertrophy. The timing of the assessment is also important as fewer patients in the pre-dialysis phase seem to be affected (182) and hypertrophy may increase with time on dialysis (chapter 4). Hypertrophy may have a higher prevalence among peritoneal dialysis patients compared with those on haemodialysis, though the study populations are small (203). Increased work of the heart is thought to be responsible (207), though a number of other risk factors

for left ventricular hypertrophy in patients with end-stage renal disease have been identified by means of multiple regression analyses: age (203), hypertension (Harnett), high serum alkaline phosphatase possibly reflecting hyperparathyroidism (203) may contribute. Anaemia (208) and excessive interdialytic weight gain (190) perhaps leading to raised atrial natriuretic peptide levels (200) have also been suggested as causes.

The pattern of hypertrophy may be concentric or less commonly asymmetric affecting the septum (190), although there is a tendency to overestimate the thickness of the septum if an oblique echocardiographic cut without the guidance of a two-dimensional scan is undertaken (206, 204). Bernardi has postulated that asymmetric septal hypertrophy is the earliest sign of myocardial involvement in uraemia (204) and may result from sympathetic overactivity as assessed by plasma adrenaline and noradrenaline levels (205). Catecholamines have also been weakly linked to myocardial dysfunction in dialysis patients (187).

Left ventricular hypertrophy in hypertensive populations (171) and people with hypertrophic cardiomyopathy (210) has been associated with an increased risk of serious ventricular arrhythmias. Patients with end-stage renal disease on haemodialysis are also undoubtedly at risk (211, 212, 213, 189, 184), despite contradictory negative findings in studies too small to draw valid conclusions (214, 215). The association between such arrhythmias and ventricular hypertrophy in end-stage renal disease however is less well defined (212), and it has been suggested that left ventricular dysfunction is a more potent risk factor (211, 184).

Patients with cardiac hypertrophy have been reported to have a greater incidence of coronary vessel disease, than those without (209) and this may in part explain the depressed myocardial function frequently observed in association with hypertrophy or arrhythmias.

Congestive cardiac failure has been described in up to ten percent of non-diabetic dialysis patients, half of whom have a hypertrophic type of cardiomyopathy and the other half a dilated picture (199) However, caution is required when interpreting studies reporting cardiac dysfunction in dialysis patients (216,185,187,188,217,218,191,219,220,193, 194,221,196,203,199,202,222) because of the effects of overhydration on preload and afterload and hence the assessment of myocardial contractility. Nevertheless, cardiac function appears to be abnormal in a significant proportion of patients at dry weight or after ultrafiltration, suggesting that other factors may influence ventricular performance.

Section 3

Ventricular influences in end-stage renal disease

As previously described (Chapter 2.2), the left ventricle hypertrophies in response to pressure or volume overload, both of which can ultimately cause left ventricular dysfunction. Not only are many of the factors (2.4.1 - 2.4.11) which produce such overload typically present in end-stage renal disease, but they can be of a marked degree and frequently occur in combination. In addition, other "ventriculopathic" factors peculiar to uraemia may contribute to cardiac hypertrophy. With replacement of renal function, the left ventricle may be exposed to further risks, such as creation of vessel access, aluminium accumulation from phosphate binding agents and dialysate. These and other "therapeutic" risks will be discussed separately (chapter 4).

3.3.1 Uraemia

Early haemodynamic studies of patients with chronic renal failure consistently identified an increased plasma volume (223, 224), though data on cardiac output conflicted. Del Greco and colleagues found cardiac output in patients with uraemia to be increased when signs of circulatory congestion were absent, but to be decreased in the presence of clinical congestive cardiac failure (223). His two groups however were not strictly comparable because of better renal function and higher haematocrits in the non-congested group. Gibson, who measured right heart pressures in patients with renal failure and acute pulmonary oedema found them to be normal or only moderately elevated, and suggested that increased pulmonary capillary permeability led to the development of pulmonary oedema in uraemia (224). Debate centred around the relative contributions of haemodynamic, myocardial and metabolic abnormalities in the pathogenesis of congestive cardiac failure and even by 1975 it was still unclear as to whether uraemia caused a specific cardiomyopathy (225). Drüeke, in a small study of haemodialysis patients was convinced of the existance of uraemic cardiomyopathy (216), yet Lewis found no evidence of such a phenomenon in patients in the predialysis phase unless severe fluid overload was present (183). Ianhez observing resolution of cardiac failure after renal transplantation also suggested uraemia had a negatively inotropic effect, but he disregarded the concomitant improvement in anaemia and hyperparathyroidism (226). Stronger evidence came from animal experiments.

Penpargkul in a study of isolated hearts from rats with and without acute and chronic uraemia, found that hearts from animals with recent

bilateral nephrectomies performed normally, as those from sham operated controls, while organs from a chronic renal failure subtotal nephrectomy model, exhibited enhanced contractility, coronary flow and myocardial oxygen consumption (227). The uraemia however was of relatively short duration, the hearts were not perfused with uraemic compounds and surprisingly the chronically uraemic hearts were no heavier, although did comprise a greater fraction of total body weight which was reduced in the uraemic animals. Using the same isolated heart model but this time from normal rats perfused with solution containing urea and other uraemic toxins, Scheuer and Stezoski, found that the rate of rise of left ventricular pressure was reduced in the presence of urea at varying concentrations (228). Such depressed contractility occured in spite of a raised end-diastolic pressure in the animals exposed to uraemic compounds, suggesting attenuation of the normal Frank-Starling effect. As coronary flow rates were lower with uraemic perfusate, diminished oxygen delivery was proposed as the mechanism. However in this experiment only the acute effects of uraemic perfusate on normal rat hearts were studied, and the concentrations of urea exceeded those found in end-stage renal failure. Similar results were obtained in a study of short-term exposure of normal guinea pig hearts to urea concentrations in a more realistic uraemic range (229).

In a study of longer term chronic renal failure in rats, Rhodes et al noted the development of myocardial hypertrophy, focal myocardial necrosis and interstitial fibrosis, but did not undertake functional studies. (230). Vascular lesions, myocardial and aortic calcification, and increased vascular permeability in the pericardium were also features.

However, the Heidelberg group were able to examine the development of myocardial fibrosis in uraemic rats in greater detail and also determine the effect of the converting enzyme inhibitor ramipril (231).

Heart weight was greater in a uraemic group compared to sham-operated controls, and by light and electron microscopy both the number and volume of interstitial cells were increased, suggesting that the cardiac hypertrophy was not myocardial. As interstitial cell nuclear size was also greater in uraemic animals these cells were assumed to be in an activated state. Non-cellular interstitial tissue was also more abundant without an apparent increase in vascular permeability, and fibrosis was shown to ultimately occur. The absence of myocardial necrosis led the authors to conclude that fibrosis was of the non-replacement type, thus challenging earlier views on ischaemic myocardial cell injury in cardiac hypertrophy. They also postulated that interstitial fibrosis in uraemia might result in reduced cardiac compliance or predispose to disturbed electrical conduction, re-entry and cardiac arrhythmias. Finally, an increased interstitial volume in ramipril treated rats, suggested that hypertension was not the mechanism responsible. The same group had previously established that heart weight in rats with renal insuffiency was increased despite normalisation of blood pressure with alpha-1-receptor or beta-1-receptor blockers, (232).

3.3.2 Hypertension

Further haemodynamic studies in uraemic patients attempted to define the effects of hypertension. Kim and colleagues confirmed earlier reports of raised cardiac indices, heart rates and systolic blood pressures in end-stage renal disease (233). However he demonstrated that derived measures of total peripheral vascular resistance were higher in hypertensive uraemic patients compared to normotensive uraemic patients and furthermore, that bilateral nephrectomy in the hypertensive patients resulted in a reduction in peripheral resistance and blood

pressure. This raised the possibility that a vasopressor substance of renal origin might cause renal hypertension, a theory which was later to be verified by recognition of the renin-angiotensin system.

In addressing the question of whether renovascular hypertension had more deleterious cardiac effects than essential hypertension, Vensel found a greater degree of left ventricular dilatation in patients with renovascular disease accompanied by reduced fractional shortening, and assymetric septal hypertrophy (234). Neither the creatinine measurements of patients with essential hypertension, nor haemoglobin concentrations for the whole group were quoted, and renovascular patients had higher systolic blood pressures. It is therefore difficult to directly compare the different groups or conclude about the impact of this form of secondary hypertension on the heart although there was a suggestion that the cardiac effects of renovascular disease were more adverse. Furthermore, these patients had only a moderate degree of renal impairment, and were still far from requiring dialysis.

Studies of patients who have reached end-stage renal failure and started on renal replacement therapy reveal that the commonest echocardiographic abnormalities are of enlargement of the cardiac chambers coupled with a moderate increase in left ventricular mass (235) To what extent hypertension contributes to these findings is unclear, although the correlation between arterial hypertension and cardiac hypertrophy has frequently been reported as weak (232,235). Some authors have suggested that the degree of hypertrophy is inappropriately low for the level of the blood pressure and chamber dilatation, and that the left ventricular hypertrophy of end-stage renal disease is "inadequate" (235). In normal subjects there is a constant relationship between arterial pressure and left ventricular mass-to-volume ratio (134), which is absent in dialysed uraemic patients. However few investigators of

uraemic patients have measured blood pressure continuously, and where this technique has been employed, data are scarce though said on trust to show that blood pressure is volume dependent (236). One of the great difficulties in studying such populations is differentiating between genuine hypertension and fluid overload, and the ideal timing of assessment in relation to haemodialysis is not clear.

Cochi measured blood pressure and left ventricular size before and after haemodialysis, in groups of patients whose background blood pressure control varied and found no significant differences between normotensives' and hypertensives' left ventricular dimensions (237). There was however a tendency for wall thickness to increase with blood pressure, and for left ventricular diameter to rise with greater interdialyctic weight gains. In contrast, Voogd did find a correlation between left ventricular hypertrophy and systolic and diastolic blood pressure, but only in anephric patients (238). He also attributed paradoxical increases in left ventricular thickness after the inception of dialysis to fluid excess.

By submitting thirty-five patients with chronic renal impairment and ten control subjects to volume expansion with one litre of saline, and monitoring their right heart pressures and in twelve left heart pressures, Jahn and colleagues found a positive correlation between cardiac index and plasma creatinine in the majority (239). However the correlation between cardiac index and haematocrit was stronger and increased further after saline infusion. Cardiac function as assessed by relating volume expansion induced changes in stroke index to changes in pulmonary capillary wedge pressure varied greatly, but decreased with the severity of renal failure, implying reduced diastolic compliance. On the other hand, systolic function, quantified in a complex fashion by simultaneous left ventricular pressure recording and echocardiographic derivation of left ventricular volume, was normal in six patients in whom

satisfactory measurements could be achieved. No comment was made about cardiac mass in this study. Golf also examined the effects of overhydration on cardiac function in haemodialysis patients: clinical congestive cardiac failure developed only in fluid overloaded patients whose hearts were additionally stressed by exercise and anaemia (240).

3.3.3 Anaemia

Subjective symptoms of dyspnoea and fatigue in chronic renal disease worsen with anaemia, and objectively the degree of impairment of aerobic and anaerobic capacity correlate directly with the severity of anaemia (241). However the precise cardiac effects of anaemia are less well understood. In anaemic subjects with normal renal function, cardiac output at rest is almost always elevated, when the haemoglobin level falls as far as 7g/dl (242, 243, 244, 245), but may be within normal limits in less severe anaemia (244). This rise is mainly the result of an increased stroke volume rather than increased heart rate, but it is blunted by age (245). An exaggerated increase in stroke volume and cardiac output also occurs in response to aerobic exercise in anaemic subjects (244, 246, 243) when compared to healthy controls and exercise may unveil altered haemodynamics in less severe degrees of anaemia (244).

Shorter circulatory times have been demonstrated in anaemic states (246, 245), though venous tone and intravascular volume will also influence the duration. Right heart pressure (243) and pulmonary arterial wedge pressure (243, 247) are normal, unless other cardiopulmonary disease is present. While plasma volume tends to be increased in anaemia (245), the total blood volume is often reduced because of diminished red cell mass (244). This, together with Fowlers study of anaemic and hypovolaemic dogs capable of generating high cardiac

outputs (248), suggests that increased preload is not the cause of augmented stroke volume.

The explanation therefore lies in the alteration of afterload, either through a change in peripheral vascular resistance or blood viscosity. Graettinger introduced the idea that reduced systemic vascular resistance was responsible for the elevation in cardiac output (244), though did not describe the mechanism. Duke and Abelmann confirmed this view by reversing the high output in anaemic patients with orthostatic stress or the vasoconstrictor drug methoxamine (245). Relative hypoxia in anaemic patients seemed a likely stimulus to vasodilatation (249).

Murray and Escobar disagreed. In their study of the effects of reducing the oxygen carrying capacity of the blood, with or without a reduction in viscosity, on cardiac output in dogs they argued that reduced whole blood viscosity was an equally if not more important contributor (250). By administering exchange transfusions of whole blood, methaemoglobin containing blood, plasma or dextran, they found the greatest increase in cardiac output to occur in animals subjected to both a lowering of oxygen carrying capacity and of whole blood viscosity. An inverse relationship between cardiac output and whole blood viscosity was supported by Weber's study of polycythaemic patients treated with radioactive phosphorous (251).

However Glick et al reported that the increase in cardiac output in anaemia was not entirely attributable to reduced whole blood viscosity, and that an intact autonomic nervous sytem was necessary for maximal elevation of cardiac output to develop in some, but not all, laboratory animals (252). Escobar also presented evidence of an enhanced ventricular contractility in acutely anaemic yet normovolaemic dogs, though was unable to conclude about the effects of sympathetic beta blockade because of the possibility of a direct cardiodepressant action of

propranolol (253). In further experiments using dogs with acute isovolaemic anaemia, improved ventricular performance at rest and during exercise was ascribed to increased sympathetic stimulation and hence myocardial contractility (254). Whether a rise in left ventricular diastolic volume leading to a Frank-Starling inotropic effect can be excluded in these studies is unclear, as is their relevence to the chronically anaemic state in man.

Are the cardiovascular responses to anaemia in chronic renal failure different? The pioneering study of Neff et al which was designed to determine whether increased cardiac output in anaemic haemodialysis patients caused hypertension, provided some answers (255). As others have also described (256, 247), cardiac output in the study population of forty haemodialysis patients was increased, with an inverse correlation between cardiac index and haematocrit apparent. Although the mean blood pressure of the group was elevated, derived peripheral vascular resistance was normal. The authors hypothesis that increased cardiac output is causally related to hypertension was refuted because the cardiac indices of hypertensive patients were no higher than those of normotensives. Furthermore, correction of anaemia by transfusion of red cells in six patients led to reduction in cardiac output in five, but a rise in diastolic and mean blood pressure. It was suggested that transfusion abolished the hypoxic vasodilatation of anaemia and resulted in a rise in arteriolar resistance and blood pressure. Neff also proposed that the anaemia of chronic renal failure might even protect patients from the adverse effects of severe hypertension (255).

However evidence from Silberberg challenges such a view. In a study of 78 dialysis patients, he found a significant relationship existed between anaemia and echocardiographic left ventricular hypertrophy (208). Using the method of Devereux and Reicheck to determine left

ventricular mass (LVM), the mean LVM index ranged from 120±8g/m^2 of the patient group in the highest quartile of haemoglobin, to 158±6g/m^2 of the group in the lowermost quartile of haemoglobin. Although, the outcome of these anaemic patients was not described, in a later paper, Silberberg demonstrated that left ventricular hypertrophy was an independent determinant of survival in end-stage renal disease (48), thereby indirectly associating anaemia with an increased risk of mortality. However, the pathogenesis of ventricular hypertrophy is likely to be multifactorial, and avoidance of anaemia by transfusion of uraemic rats does not prevent an increase in heart weight (232).

3.3.4 Hyperparathyroidism

One of the complications of chronic renal failure, arising as a result of phosphate retention and relative deficiency of 1,25-dihydroxy-vitamin D_3, is secondary hyperparathyroidism. As a consequence of increased parathyroid hormone (PTH) secretion, bone resorption and turnover is stimulated and serum calcium levels rise. In the presence of high serum phosphate concentrations, deposition of calcium phosphate in soft tissues and blood vessels is favoured.

Milligan, in a comprehensive review of metastatic calcification, gathered reports of 23 patients with chronic renal disease in a predialysis era, who at post mortem were found to have widespread tissue calcification (257). Eleven had cardiac calcification, most marked in the left ventricle, but not all had parathyroid hyperplasia. Terman suggested that moderate to severe cardiac calcification may result in disturbances of conduction such as varying degrees of heart block (258). Others have reported marked and rapidly progressive calcification of the left-sided heart valves, particularly the mitral, sufficiently severe to cause functional

impairment (259, 260). In a larger echocardiographic study of 87 older haemodialysis patients, Maher and colleagues found calcification of the aortic valve in 24 (28%) patients, and of the mitral annulus in 31 (36%) (261). Six patients, five with aortic disease had significant valvular stenoses, although clinical murmurs were a poor guide to their presence. The changes were attributed to abnormal calcium and phosphate metabolism, as the calcium-phosphate products in affected patients tended to be higher, and also to increased mechanical stress upon the valves. The risk of infective endocarditis in such patients is not known.

Myocardial calcium, as assesed by the technique of energy subtraction radiology, was estimated and related to echocardiographic left ventricular ejection fraction in 43 dialysis patients and 32 controls (262). The myocardial calcium content was higher in uraemic patients and was significantly and inversely related to ejection fraction, thus implying calcium depostion has a cardiodepressant effect. Ejection fraction was also directly related to PTH concentration, but there was no association between myocardial calcium content and PTH. Multiple regression analyses revealed positive correlations between myocardial calcium content and calcium-phosphorous product, vascular calcification, colour (black) and previous parathyroidectomy.

Although these studies suggest a role for PTH in the pathogenesis of uraemic left ventricular disease, its specific effects have only been studied in animal experiments. Bogin et al examined the responses of cultured rat heart cells to intact PTH, amino-terminal (1-34) and carboxy-terminal (53-84) PTH (263). Only the intact and N-terminal molecules produced responses; an immediate and sustained rise in heart rate and early cell death.These actions were assumed to be mediated through calcium entry into the cell because they required calcium and could be mimicked by a calcium ionophore and blocked by the calcium antagonist

verapamil. Furthermore exposure of the cultured cells to uraemic rat sera caused similar effects only if the donor animals had parathyroid tissue (263). Katoh also documented the positive intropic action of PTH (264), but later work from Massry's group was contradictory, as it demonstrated calcium dependent inhibition of cardiac mitochondrial respiration by chronic PTH administration in rats, leading eventually to a decrease in cardiac output (265).

Kraikipanitch demonstrated that both the calcium content of the myocardium and muscle mass are increased in uraemic dogs retaining pararthyroid tissue, and similar findings have been reported in rats (266, 232). However the development of cardiac hypertrophy is not prevented by parathyroidectomy before the induction of renal failure and is therefore not dependent on PTH alone (232). Nor is the rise in heart calcium in renal failure, solely mediated by PTH (232).

Some authors have suggested that accumulation of calcium in myocardial cells might be harmful because catecholamine stimulated calcium entry can cause necrosis (267). There is no direct evidence of such an effect in uraemia, although early studies did identify PTH dependent calcium deposits in the myocardium and coronary arteries of rats rendered uraemic (268). It is more likely that calcium acts as an early stimulus to DNA synthesis and cell growth (269). In the Syrian hamster model of hypertrophic cardiomyopathy, myocytic calcium levels are elevated (270), and development of the condition is retarded by treatment with the calcium channel blocker, verapamil (270). In contrast, administration of a calcium ionophore to pregnant rats results in cardiac hypertrophy characterised by myofibrillar disarray (127).

PTH has other effects which could influence left ventricular morphology and function: It has vasodilator properties and causes hypotension in a dose dependent fashion when injected intravenously into

rats and dogs (271). While many visceral vascular beds including the heart and kidney are affected, skeletal muscle is not. Intracellular cAMP is involved and preliminary evidence points to blockade of calcium entry into vascular smooth muscle as the mechanism (272). The cycloxygenase inhibitor, indomethacin attenuates this hypotensive response suggesting prostaglandins may also mediate PTH induced vasodilatation (273). It is believed that the vascular and hypercalcaemic actions of PTH are separate and arise from different parts of the molecule (272).

PTH therefore has the potential to modify cardiovascular responses and cardiac composition, yet evidence of its effects in human chronic renal disease is conflicting. London compared the echocardiographic findings in haemodialysis patients with and without secondary hyperparathyroidism, as judged by the degree of bone resorption on biopsy, and also looked at healthy controls (274). He found that haemodialysis patients with normal bone resorption had both an increased left ventricular volume and mass compared to controls, but equivalent mass-to-volume ratios. In contrast, patients with bone biopsy evidence of hyperparathyroidism had only left ventricular dilatation and hence lower mass-to-volume ratios. These patients also had higher heart rates and echocardiographic features to suggest augmented contractility, which led the authors to suggest that parathyroid hormone might have myocardial effects and prevent the development of "adequate" ventricular hypertrophy. Jahn, too, observed increased myocardial contractility in patients with renal impairment and hyperparathyroidism, particularly after volume loading, and through a contrived series of calculations correlated responsiveness of the myocardium to increased load with the ratio of extracellular ionized calcium to extracellular potassium (239). Although these results seem to contradict much of the animal work and Rostands

view that hyperparathyroidism in humans is associated with depressed cardiac function (262), a crucial difference is that myocardial calcium content in the better performing hearts was not measured. Perhaps it is myocardial calcium rather than PTH that has the negative inotropic effect.

Further indirect evidence for the unfavourable effect of hyperparathyroidism, was presented by Lai, who found that cardiac performance in haemodialysis patients improved with long-term administration of cimetidine (275). He attributed this to suppression of uraemic hyperparathyroidism by the H_2 antagonist, although could not discount a direct cardiac or vasodilatory action. Drüeke, who noted an increase in contractility and cardiac ouput in haemodialysis patients within two weeks of parathyroidectomy, also concluded that excess parathyroid hormone was harmful to the myocardium (276). Such findings were not reproduced in smaller studies of haemodialysis subjects before and after parathyroidectomy (277, 278). However by employing three different methods to achieve a reduction in PTH, namely parathyroidectomy, treatment with 1,α-hydroxycholecalciferol, or manipulation of serum magnesium, McGonigle was able to demonstrate some small improvement in echocardiographic cardiac function with each manoeuvre (279). It was not clear to what extent the changes could be ascribed to alterations in calcium or magnesium concentrations or the effects of the vitamin D analogue rather than PTH. 25-hydroxy-vitamin D_3 treatment in haemodialysis patients is associated with a fall in PTH levels and an improvement in left ventricular function (280). However it could be argued that relative vitamin D deficiency which is known to cause hypotonia of skeletal muscle, is also responsible for myocardial dysfunction, and that PTH concentration is irrelevant

3.3.5 Other factors

It has been suggested that chronic acidosis may compromise ventricular function possibly through a reduction in coronary blood flow (281). Although the cardiac effects of longstanding acidosis in renal failure are unknown, short term studies of acid-base changes induced by dialysate buffers show no significant findings (4.4).

However, administration of ascorbic acid may predispose to oxalic acid synthesis, and widespread deposition of calcium oxalate. A case of myocardial calcinosis complicating hyperoxalaemia in a dialysis patient who died of cardiac failure has been reported (282).

Vitamin deficiency is a more common problem among patients with renal failure, and Gotlieb, describing a patient with beri-beri, proposed thiamine should be measured in all dialysis patients with heart failure but no signs of fluid overload (283).

Patients receiving renal replacement therapy might also be at risk of developing cardiomyopathies secondary to selenium defiency (284) and hypokalaemia (285).

The 21-amino acid polypeptide, endothelin, is a potent vasoconstictor with the potential to influence both systemic and renal haemodynamics. It has been implicated in the pathogenesis of experimental acute renal failure (286), and elevated levels have also been described in chronic renal failure (287). Endothelin values are even higher in hypertensive haemodialysis patients (288), a group at risk of developing severe left ventricular hypertrophy. However, further study is necessary to determine whether endothelin plays a role in the pathogenesis of cardiac hypertrophy in end-stage renal disease.

Chapter 4

THE INFLUENCE OF TREATMENT FOR CHRONIC RENAL FAILURE ON THE LEFT VENTRICLE

As well as the effects of uraemia, hypertension, and hyperparathyroidism, the heart may also be subjected to additional stresses in the form of renal replacement and other therapy.

Section 1

Effects of Arteriovenous Fistulae on the Left Ventricle

It is widely recognised that patients with arteriovenous shunts have increased cardiac outputs, stroke volumes and end-diastolic pressures. Renal failure patients who already may have hyperdynamic circulations because of fluid overload or anaemia are similarly affected, and several studies of the change in cardiac output induced by occlusion of arteriovenous shunts or fistulae in haemodialysis patients have shown significant reductions (289, 290, 291, 292). Neither the type of shunt, nor its age appear to influence the degree of elevation of cardiac output (290, 291) and congestive cardiac failure can develop (289). The assessment of the size of the shunt or fistula, in which blood flows may exceed one litre per minute (291, 292), will not reliably identify patients at risk of cardiac failure, perhaps because these people often have additional problems such as impaired left ventricular function or septal hypertrophy (291). However, selected patients can benefit from permanent fistula closure (289).

The principle mechanism which brings about a fall in cardiac output on temporary occlusion of fistulae is a reduction in heart rate (291) which

has found application as a clinical test of excessive shunting, known as the Nicaladoni-Branham sign.

In laboratory experiments in rats without renal failure, shunting through either femoral or aortocaval fistulae produces myocardial cell enlargement, principally elongation and hence eccentric cardiac hypertrophy (293).

Section 2
Haemodialysis and the Left Ventricle

Much has been written about the effects of haemodialysis upon the left ventricle. Various techniques ranging from echocardiography to radionuclide ventriculography have been applied and varying conclusions reached.

4.2.1 Ventricular structure and systolic function

Assessing any impact of haemodialysis on the myocardium is difficult because so many other aspects of the uraemic state (chapter 3) exert effects. Although hypertrophy is often marked at the outset of treatment (294) (figure 4), long term studies of haemodialysis patients have shown left ventricular muscle thickness, particularly interventricular septal width, increases in size with duration of dialysis dependence (295, 202). The left atrial diameter also progressively enlarges, suggesting the development of diastolic dysfunction (202). Only age has been identified as a specific risk factor predisposing to left ventricular hypertrophy among haemodialysis patients, although blood pressure tends to be higher when left ventricular hypertrophy is present (203, 188). The length of each dialysis session seems not to influence the morphology of the left

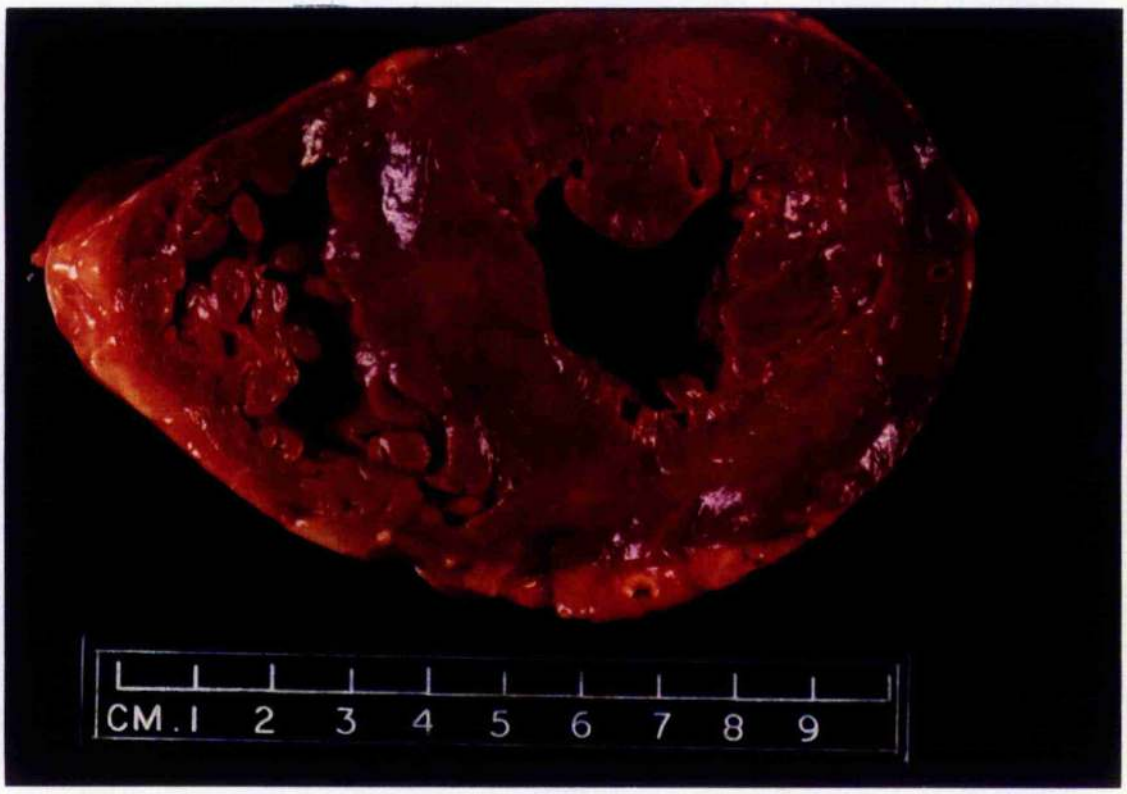

Figure 4

Post-mortem section of the heart of a 70 year old man with renovascular disease who died suddenly, shortly after commencing haemodialysis. Marked left and moderate right ventricular hypertrophy are evident

ventricle (202), but dialysis itself may lead to an imbalance between myocardial oxygen supply and demand and result in myocardial underperfusion (296).

A common approach has been to examine the systolic function of the left ventricle before and after haemodialysis, and assume any change is the direct consequence of the dialysis procedure and removal of cardiodepressant uraemic toxins. In this way, several authors have concluded that haemodialysis has the beneficial action of improving myocardial contractility (297, 189, 194, 192, 218, 222, 296). The measurements from which such conclusions were drawn include the echocardiographic indices, ejection fraction, fractional shortening and velocity of circumferential fibre shortening (V_{Cf}). All are derived from the measurement of end-diastolic and end-systolic diameters and for V_{Cf}, left ventricular ejection time.

Dialysis which includes ultrafiltration or produces vasodilatation will lead to a reduction in circulating blood volume and preload and hence smaller ventricular dimensions. Changes in loading conditions therefore may be erroneously interpreted as improved contractility, although a genuine inotropic effect cannot be discounted. Similarly, studies which have attempted to draw distinctions in the response to dialysis between patients with and without cardiac failure can also be criticised because of deviations from dry weight (196, 194). Not all investigators have misinterpreted such changes. Others have recognised that load-induced changes in left ventricular end-diastolic pressure may invalidate these echocardiographic indices and spuriously point to enhanced contractility with haemodialysis (185, 196, 219, 217, 197, 298). Vancheri has even used the changes in echocardiographic left ventricular diameters in conjunction with phonocardiography to determine the effects of volume reduction through haemodialysis on diastolic time intervals and hence left

ventricular filling time (299). Not only did this study highlight the influence of loading conditions on left ventricular size, but it demonstrated a prolongation of the isovolaemic relaxation time with dialysis for any given R-R interval, thus implying less good diastolic function.

The difficulties of assessing left ventricular systolic function by means of echocardiography were reviewed by Tomson (300) and have been addressed in studies of isolated ultrafiltration without dialysis and of isovolaemic dialysis. In order to dissociate the effects of changes in filling pressure from removal of uraemic toxins, Nixon et al undertook serial echocardiography across haemodialysis with and without weight loss and ultrafiltration (301). They confirmed that fluid loss through ultrafiltration alone caused a reduction in end-diastolic volume and stroke volume, without affecting end-systolic volume or V_{cf}, a true Frank-Starling response. Following haemodialysis, without manipulation of volume, biochemical improvements were accompanied by a decrease in end-systolic volume and increases in stroke volume, ejection fraction, and V_{cf}, all signifying a genuine rise in contractility. The same group also examined the effects of different types of dialysate on cardiac function.

4.2.2 Dialysate and ventricular function

If haemodialysis is associated with an improvement in cardiac contractility, is this because of removal of a dialysable uraemic toxin or addition of an inotropic agent? In order to correct metabolic acidosis of renal failure during haemodialysis it is necessary to include a buffer in the dialysate. Sodium acetate which in vivo is metabolised to bicarbonate was the first to be employed, but causes a marked rise in serum acetate levels in approximately twenty-five percent of patients who are slow metabolisers (302). As acetate has a vasodilatory action and produces a

tachycardia, it may predispose to intradialytic hypotension (303,302), although evidence supporting a specific cardiodepressant action is conflicting (304).

When developments in dialysate production permitted bicarbonate to be used as an alternative buffer, this was claimed to be superior agent, less likely to cause nausea, tachycardia, relative hypoxaemia, or left ventricular dysfunction (305, 303, 220, 306). Patients with impaired left ventricular function were said to experience a greater increase in contractility with bicarbonate dialysis than with acetate, although once more the influence of preload on echocardiographic indices of systolic function was in disregarded (307). Anderson and Mehta who investigated isovolaemic dialyses, in albeit small numbers of stable patients, overcame this problem and contradicted reports of acetate's cardiodepressant properties (308, 309). They found that both dialysis buffers caused comparable increases in left ventricular contractility, at least in their small groups of patients without heart failure (308,309). Krishna on the other hand, who used the ratio of end-systolic pressure to end-systolic volume as a load independent index of myocardial contractility in eight patients, found no significant change in systolic function with either acetate or bicarbonate, though there was a tendency for the ratio to fall and inclusion of more patients might have altered the conclusion (221). In clinical practice bicarbonate is the preferred buffer, particularly if patients have a history of cardiac disease or instablilty during haemodialysis.

The underlying mechanism for any inotropic effect is not yet clear, although Nixon's group in another pioneering study of isovolaemic dialysis, found that changes in cardiac function were most closely related to an increase in plasma ionised calcium (310). Neither the incomplete removal of uraemic toxins, nor a rise in serum bicarbonate concentrations

achieved the same degree of improvement, but noradrenaline levels were higher both before and after calcium manipulation, an important factor about which the authors made no comment (310). Nevertheless, others have observed an improvement in myocardial performance after correction of low extracellular ionised calcium levels (311, 312), suggesting the effect is indeed genuine.

The significance of changing prostaglandin concentrations during dialysis is unclear (313), but might predispose to haemodynamic instability.

4.2.3 Haemodialysis and arrhythmias

Another factor which favours dialysis hypotension is the disturbance of cardiac rhythm. Not only are ventricular arrhythmias more common among patients with end-stage renal disease (Chapter 3.2.1), but they frequently occur during and up to ten hours after the dialysis procedure itself (211, 314, 213). Use of low potassium dialysate may exacerbate the problem (314), while reduction in oxygen delivery could also contribute (296), especially as hypertrophied ventricles appear more susceptible (212). In addition, the incidence of first degree heart block may increase with the number of years of dialysis treatment (212). The influence of low serum calcium on arrhythmias is uncertain, but the temporal relationship with dialysis would argue against an association.

Section 3
Peritoneal Dialysis and the Left Ventricle

There are fewer studies of the heart in patients receiving the newer type of dialysis, continuous ambulatory peritoneal dialysis (CAPD), and

the results are conflicting. Leenan suggested that because hypertension is often better controlled with CAPD, left ventricular mass should fall (315). With a cube formula, he was able to demonstrate a reduction in mass, attributable to a reduction in left ventricular wall thickness and more importantly to a decrease in end-diastolic dimension in fourteen of fifteen hypertensive CAPD subjects. He did not explore the impact of this internal cavity change on the derived left ventricular mass or systolic function (315) . He also failed to relate left ventricular mass to patient weight, which frequently increases with CAPD treatment because of the absorption of glucose from intraperitoneal dialysate. Nor did he discuss the degree of anaemia in his patients. Similar reversal of hypertrophy was reported by Deligiannis, who followed ten CAPD patients for a mean of twenty-two months during which time the mean haemoglobin rose (295)

In contrast, Eisenberg who did take account of weight, and used similar methods to determine left ventricular mass, found that there was a tendency for hypertrophy to increase with ongoing dialysis (316). It is perhaps relevant that blood pressure and haemoglobin remained unchanged after the introduction of CAPD and only systolic blood pressure correlated significantly with the degree of left ventricular hypertrophy. Patients with severe hypertrophy had a high mortality.

More recently Hüting et al concluded that left ventricular hypertrophy in CAPD patients was not the result of hypertension, but related to hyperdynamic circulations and inefficient dialysis (317). The latter conclusion is unsubstantiated and large studies comparing the cardiac consequences of CAPD and haemodialysis are lacking.

Section 4

Renal Transplantation and the Left Ventricle

One of the earliest studies of cardiac function in patients with renal transplants proved to be most useful in that it demonstrated that haemodynamic measurements in transplant recipients were no different from those of healthy controls (233). Cardiac indices after transplantation, despite a slightly lower mean haematocrit, were normal. Furthermore, a comparison of hypertensive and normotensive transplanted patients revealed similar blood volumes, plasma renin concentrations and renal function, thereby indicating that increased peripheral vascular resistance must be responsible for raised blood pressure (233). However the precise cause was not clear. Correction of anaemia was assumed to be the main factor in leading to resolution of the high output state characteristic of end-stage renal failure.

Since then a number of other findings have been described. The prevalence of left ventricular hypertrophy in patients with renal allografts, as assessed by a variety of echocardiographic measures, is consistently reported at around forty percent, lower than in dialysis populations (203,318). Despite this, electrocardiographic appearances may remain unchanged (319). With only one exception (320), serial studies of left ventricular morphology across renal transplantation have agreed, by which ever echocardiographic criteria were employed, that left ventricular mass falls significantly (321, 322, 295, 323, 324). This occurs early, within the first three to six months (323, 324), and although it coincides with a return to a euvolaemic state, there has been a tendency for investigators to neglect the significance of concurrent events or their influence upon echocardiographic indices.

Instead authors have sought risk factors for hypertrophy after transplantation and identified only the number of antihypertensive agents required and therefore by implication, raised blood pressure (323, 318, 203). Hypertension is more common than might be anticipated after restoration of renal function. As many as sixty-five percent of patients may require antihypertensive treatment in the post-transplant period because of steroid and cyclosporin treatment, diseased renin-secreting native kidneys, ongoing renal impairment (perhaps as a consequence of chronic rejection), and development of stenosis in the transplant renal artery (325).

Many studies have also described improved systolic ventricular function following renal transplantation (320, 319, 295, 324), which would accord with the lower incidence of cardiac failure in transplant patients (6). Case-reports have even cited partial or complete resolution of intractable cardiac failure after transplant surgery and attributed this to the elimination of uraemic toxins, although the authors cannot discount the possibilty that the cardiac failure was due to fluid overload (326). Ikäheimo has suggested that the response of cardiac function to renal transplantation can be predicted by the improvement which results from weight removal through haemodialysis (321). Similarly the transplant mediated alleviation of the adverse effects of anaemia and hyperparathyroidism have often been disregarded.

In contrast, diastolic ventricular function may remain impaired after successful renal transplantation and continue to pose the risk of pulmonary oedema, in spite of regression of left ventricular hypertrophy (324).

Section 5

Drugs and the Left Ventricle

The actions of many drugs which influence the morphology or function of the left ventricle, might plausibly be potentiated if drug elimination is delayed as a result of renal failure. In practice, the evidence for this is limited, and with appropriate dosing, the cardiac effects of drugs should be assumed to be unchanged. These include regression of left ventricular hypertrophy in hypertension with methyl dopa, clonidine, ß-adrenergic receptor blocking agents, angiotensin converting enzyme inhibitors and certain calcium channel blocking drugs (327, 328). Such reversal may occur independently of a blood pressure lowering effect (327). Vasodilator treatment on the other hand can lead to an increase in cardiac mass (327).

However several drugs deserve attention because of their widespread use in patients receiving renal replacement therapy.

4.5.1 Beneficial therapy

As well as causing regression of ventricular hypertrophy, it has been suggested that calcium channel blockade with verapamil may reduce the incidence of dialysis related hypotension in patients with left ventricular hypertrophy and presumed diastolic dysfunction (329).

4.5.2 Adverse therapy

It is of concern that a number of agents may have the potential to increase cardiac mass in patients with end-stage renal failure.

Aluminium loading through use of aluminium containing phosphate binders, has been associated with cardiac hypertrophy in haemodialysed patients (330) and this in turn might be related to intradialyctic hypotension or even sudden cardiac death (331).

Repeated blood transfusion in anaemic uraemic patients also poses the theoretical risk of haemosiderosis involving the myocardium, though evidence to support this view is lacking.

Cyclosporin constitutes a greater risk: as well as having adverse vascular side-effects, this first-line immunosuppressive agent may cause hypertension and left ventricular hypertrophy, at least in cardiac transplant recipients (332). As most of the studies demonstrating regression of cardiac hypertrophy after renal transplantation were undertaken in the pre-cyclosporin era, the importance of this action is not known.

Another drug with hypertension as a side-effect is erythropoietin. One of the questions, this thesis will address is whether the beneficial effects on the heart of treating anaemia with erythropoietin outweigh the risks of increased blood pressure and viscosity.

Beta adrenergic blocking agents may impede the expected improvement in systolic function associated with haemodialysis in patients with increased muscle mass (333).

Chapter 5

AIMS AND METHODS

Section 1
Aims of this thesis

The main aim of this thesis was to investigate prospectively the prevalence of left ventricular hypertrophy in patients with end-stage renal failure selected for renal transplantation and to assess the influence of transplantation on left ventricular morphology and function using approved echocardiographic and Doppler techniques. In addition the influence of left ventricular mass on the outcome of patients presenting for renal transplantation was studied.

As renal transplantation not only corrects uraemia, but also commonly leads to the reversal of anaemia and hyperparathroidism, some of the first patients to be treated with the new drug recombinant human erythropoietin and patients scheduled for subtotal parathyroidectomy served as control groups.

5.1.1 Study subjects - rationale

The principle group studied comprised a consecutive series of adults about to undergo renal transplantation at the Western Infirmary renal unit in Glasgow between January 1988 and July 1990. As echocardiography was performed by the author alone and only with informed consent of the patients according to the local ethical commitee's guidelines, the series was unavoidably incomplete. One hundred and fifty three (67%) of a possible 228 pre-transplant echoes were obtained.

During the course of this study, the unit became involved in a double-blinded, placebo controlled trial of the value of the prostaglandin analogue Misoprostol in preventing early renal allograft dysfunction. The author was responsible for patient recruitment and supervision. Although this drug has no known cardiac effects, prostaglandin analogues can cause peripheral vasodilatation and could therefore potentially affect blood pressure and left ventricular mass. Hence a comparison of treated and untreated patients was made.

Some unexpected findings in the course of the study led to questions about the influence of volume overload on echocardiograhic indices, so in order to determine whether reduction in circulating volume affects measurement of left ventricular mass in patients with end-stage renal failure, echocardiography was performed before and after haemodialysis with ultrafiltration.

5.1.2 Presentation

The findings of these separate studies will be presented and discussed as follows:

Chapter 6	The left ventricle in a dialysis population
Chapter 7	Renal transplantation and the left ventricle
Chapter 8	Anaemia and the left ventricle
Chapter 9	Hyperparathyroidism and the left ventricle
Chapter 10	Discussion

Section2

Methods

As the techniques applied to the various study populations are similar, they will be described only once.

5.2.1 Patients

All patients were seen by the author, who explained the nature of the study, sought permission according to the local ethical committee's guidelines, and obtained a full medical history. She undertook general and cardiovascular examinations, obtained blood for biochemical, haematological and in some cases, rheological measurements, and then performed echocardiographic and Doppler examinations.

5.2.2 Blood pressure

Blood pressure was measured on the day of echocardiography using a standard mercury sphygmomanometer after five minutes with the patient in a seated position. Routine drug treatment was not discontinued beforehand because of the unpredictabilty of the timing of cadaveric renal transplantaion and the importance of good blood pressure control in more elective live donor transplanatation. As blood pressure measurement immediately before surgery may not be representative, the average of this and the two most recent clinic or pre-dialysis blood pressure recordings was calculated. Mean blood pressure on the day of echocardiography was also determined according to the formula:-

Mean pressure = diastolic pressure + pulse pressure/3

5.2.3 Body Surface Area

Patients heights (cm) were recorded and their weights (kg) measured without outdoor clothing or shoes. Body surface area (bsa) was determined according to Boyd's formula and expressed in m^2:

$$bsa = 3.2 * ht^{0.3} * wt^{[0.7285-0.0188*\log10 (wt)]}/10^4 \ m^2$$

where ht = height in centimetres
wt = weight in grams
* = multiplied by

5.2.4 Biochemical measurements

Urea, electrolytes, calcium, total protein, albumin, phosphate, and alkaline phosphatase were all measured on a SMAC-1 (Technical Instruments Corporation, Basingstoke, UK). The total serum calcium values were corrected for albumin concentration using the formula:

$$Calcium_c = calcium_m + 0.02\ (40 - albumin_m)$$

where $Calcium_c$ = corrected calcium
$Calcium_m$ = measured calcium
$Albumin_m$ = measured albumin

Serum parathyroid hormone was measured with a two site immunometric assay for intact (1-84) parathyroid hormone using

monoclonal antibodies. All laboratory normal ranges are give in Appendix 1.

5.2.4 Haematological measurements

Haemoglobin was measured with an automated Coulter counter (Coulter S Plus IV 3D).

5.2.5 Rheological measurements

Whole blood viscosity and plasma viscosity were measured by Ms Karen McLaughlin of Department of Medicine, Glasgow Royal Infirmary on a rotational viscometer, within 6 hours of the blood sample being withdrawn into an EDTA tube. The measurements were made at a temperature of 25°C and at high shear rates of $200s^{-1}$. The SI unit of viscosity is the milli-pascal-second (mPa.s)

The corrected viscosity represented the viscosity corrected to a standard haematocrit of 0.45 (BBC microcomputer and programme), while the relative viscosity was calculated from the ratio corrected viscosity/plasma viscosity.

5.2.6 Echocardiographic and Doppler Examinations

M-mode and two dimensional (2-D) echocardiography and Doppler assessments were all undertaken by the author using a Hewlett-Packard ultrasound unit (model 77020A) with a 2.5 MHz transducer. Patients were studied in the left decubitus position with the transducer in the third to the fifth intercostal space. 2-D echocardiography permitted simultaneous

visualisation of the left ventricular cavity and hence accurate positioning of the M-mode cursor. Both 2-D and M-mode scans were recorded on video and an M-mode record was also taken on six inch light-sensitive paper with a paper speed of 50mm/second. These paper records were then coded so that the identity of the patient and the timing of the scan was unknown to the author when later analysing the traces.

Only echocardiographic frames with clear images and continuous lines were deemed suitable for analysis, which was performed using a digitising tablet (Kontron Ltd) and a microcomputer (Cardio 80). These instruments report dimensions to two decimal points, but for the purpose of tabular representation of wall thicknesses only one decimal point was quoted. The measurements are discussed in 5.3.1.

As is frequently reported in echocardiographic research, it is often possible to obtain satisfactory recordings in one "view", but not another in the same individual. Hence a complete data-set was not always obtained for every patient.

Mitral flow was sampled using a 2.5 MHz transducer modified to deliver and receive doppler signals, and was recorded on light-sensitive paper. The peak velocities from early "passive" ventricular filling (the E wave) and later "active" ventricular filling from atrial contraction (the A wave) were measured with a ruler by the author on recordings coded for anonymity (figure 5) (165).

With the exception of pre-transplant and post-dialysis assessments, all echocardiography in haemodialysis patients was undertaken immediately before a haemodialysis session.

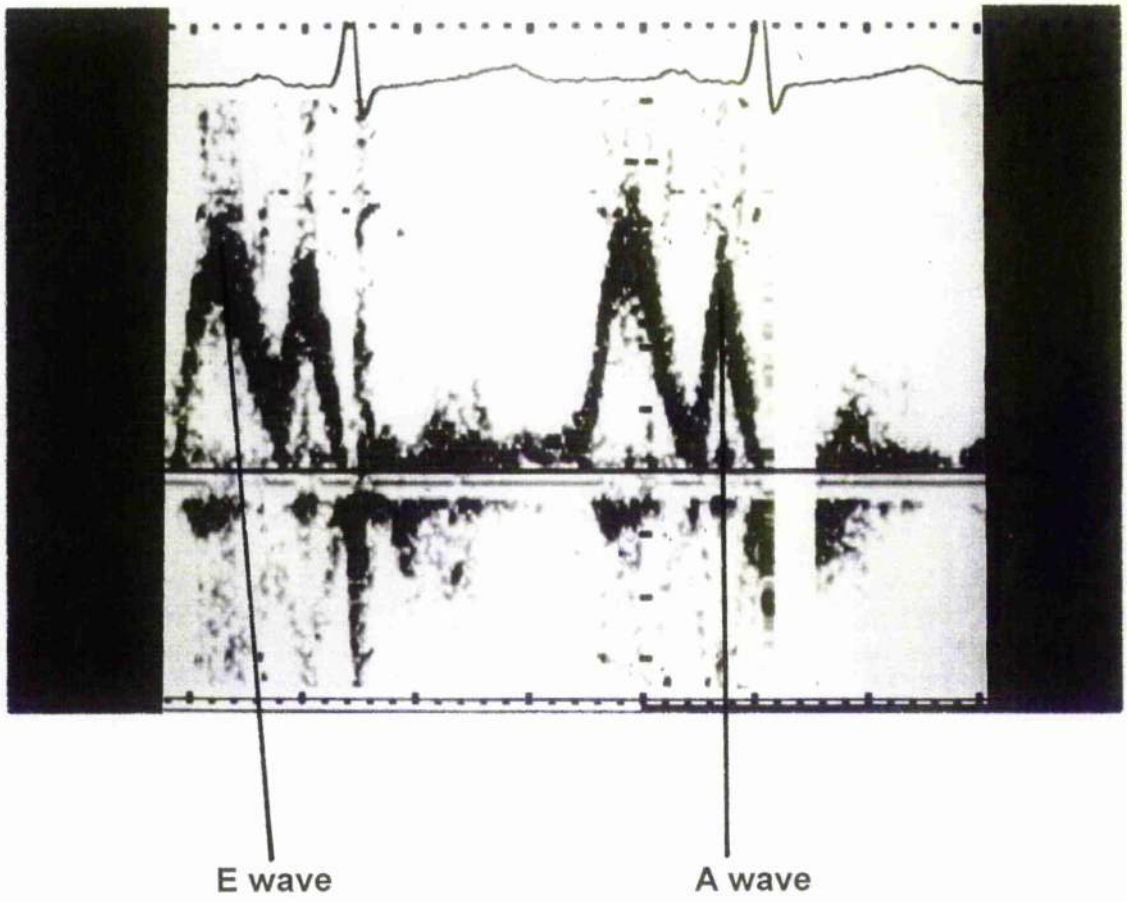

Figure 5

Doppler recording of transmitral flow. the E wave is the early velocity peak due to passive ventricular filling and the A wave is due to atrial contraction

Section 3

Echocardiographic measurements

5.3.1 Left ventricular dimensions

The interventricular septal thickness (IVST), the left ventricular internal dimension (LVID) and posterior wall thickness (PWT) were all measured just distal to the tips of the mitral valve leaflets at the end of diastole, represented by the peak of the 'R' wave on a simultaneous ECG recording (Figure 6). IVST included the endocardial layers on either side of the interventricular septum, while the endocardial, but not the pericardial surface of the posterior left ventricular wall was regarded as contributing to PWT. Measurements of IVST, LVID and PWT were made over three consecutive cardiac cycles and the mean values calculated.

Left ventricular wall thickness at post mortem has been shown to be similar to echocardiographic PWT and IVST in systole but greater than wall thickness in diastole (334), perhaps because hearts at necropsy are in the systolic phase of the cardiac cycle, while echocardiographic measurements are made during diastole. As left ventricular mass determinations are not subject to such discrepancies, hypertrophy may thus be better assessed.

The mean echocardiographic wall thickness (MWT) was also determined according to the formula:-

$$MWT = (IVST + PWT)/2$$

Relative wall thickness (RWT) was calculated thus:-

$$RWT = 2PWT/LVID$$

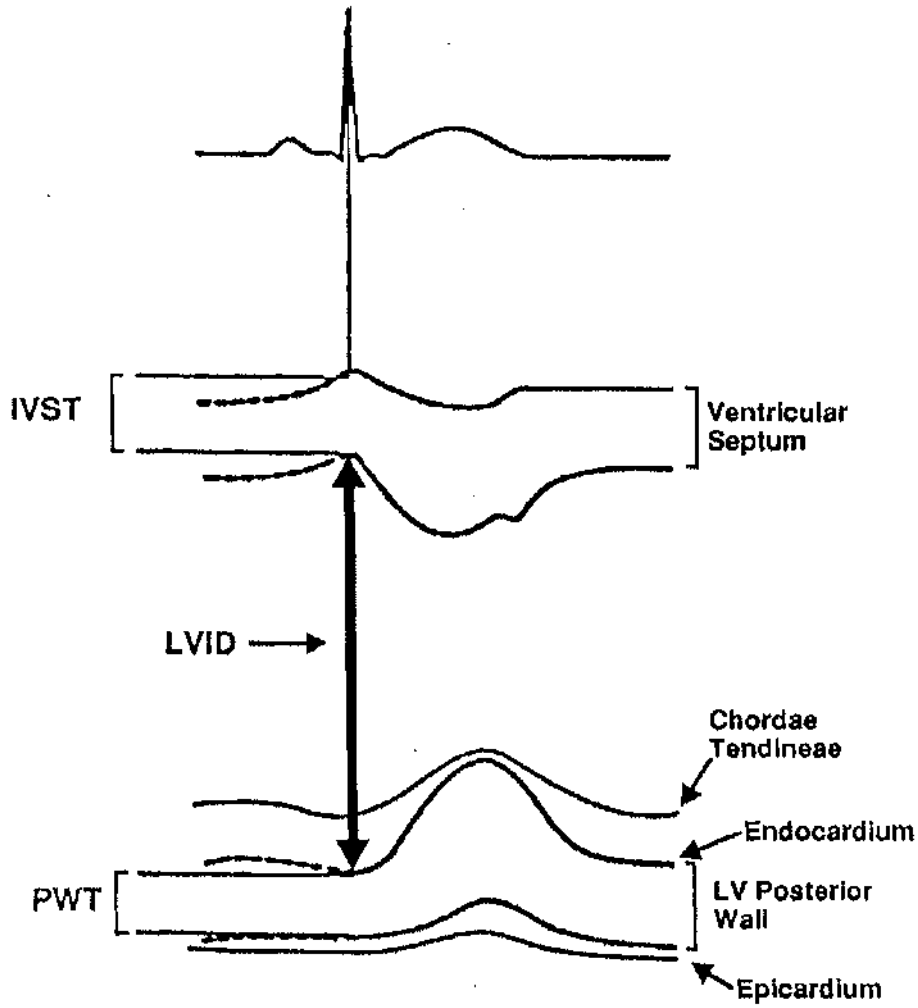

Figure 6

Diagram of the left ventricular dimensions measured by M-mode echocardiography

5.3.2 Left atrial diameter

The maximum diameter of the left atrium at the end of ventricular systole was measured, as recommended by the American Society of Echocardiography (335) (figure 7). This may be valuable as indirect evidence of left ventricular diastolic dysfunction (336).

5.3.3 Left ventricular mass

Apart from consideration of wall thickness, a number of methods of calculating left ventricular mass have been described. However, only Devereux and Reichek's method (51) has been anatomically validated by post-mortem measurement of left ventricular weight and therefore their M-mode modified cube formula was chosen as the preferred method in this study.

It comprises a cube formula which incorporates the Penn convention of excluding endocardial widths from the measurements of the interventricular septum and posterior wall and including endocardial thickness in the measurement of the LVID (Figure 8). The derived volume of the left ventricular cavity is subtracted from the total derived left ventricular volume, and corrected for the specific gravity of muscle, as follows.

$$LVM\ (g) = 1.04([LVID_p+PWT_p+IVST_p]^3-[LVID_p]^3) - 13.6$$

where 1.04 = density of myocardium

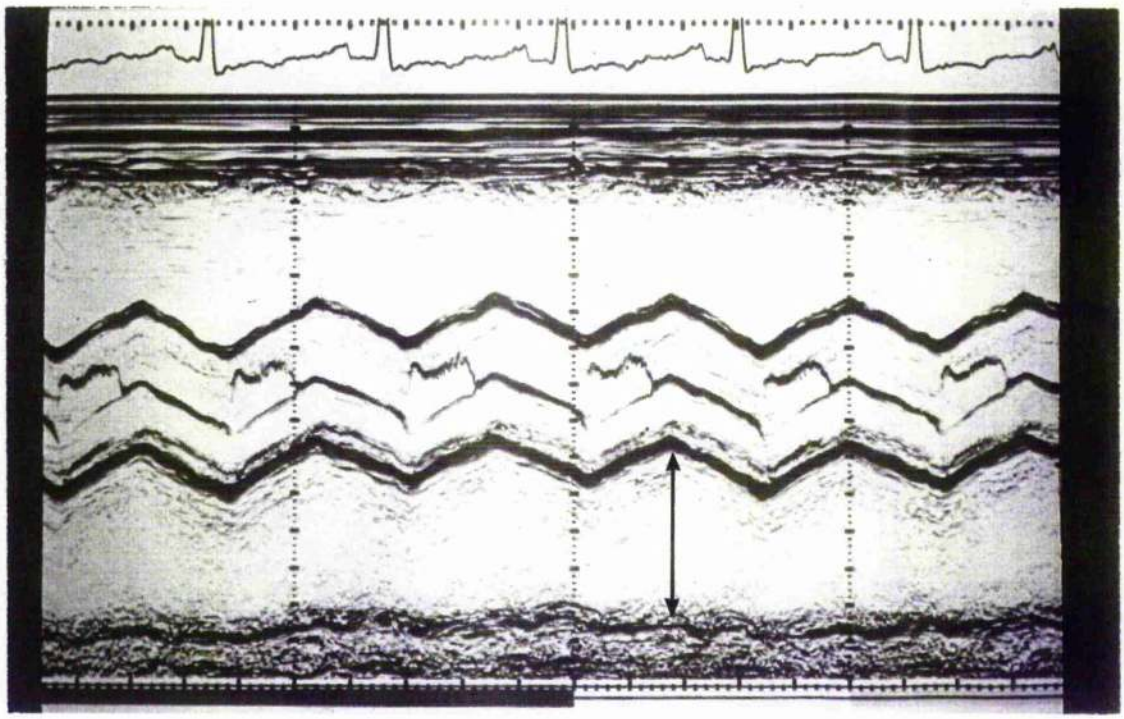

Figure 7

M-mode echocardiographic assessment of left atrial diameter

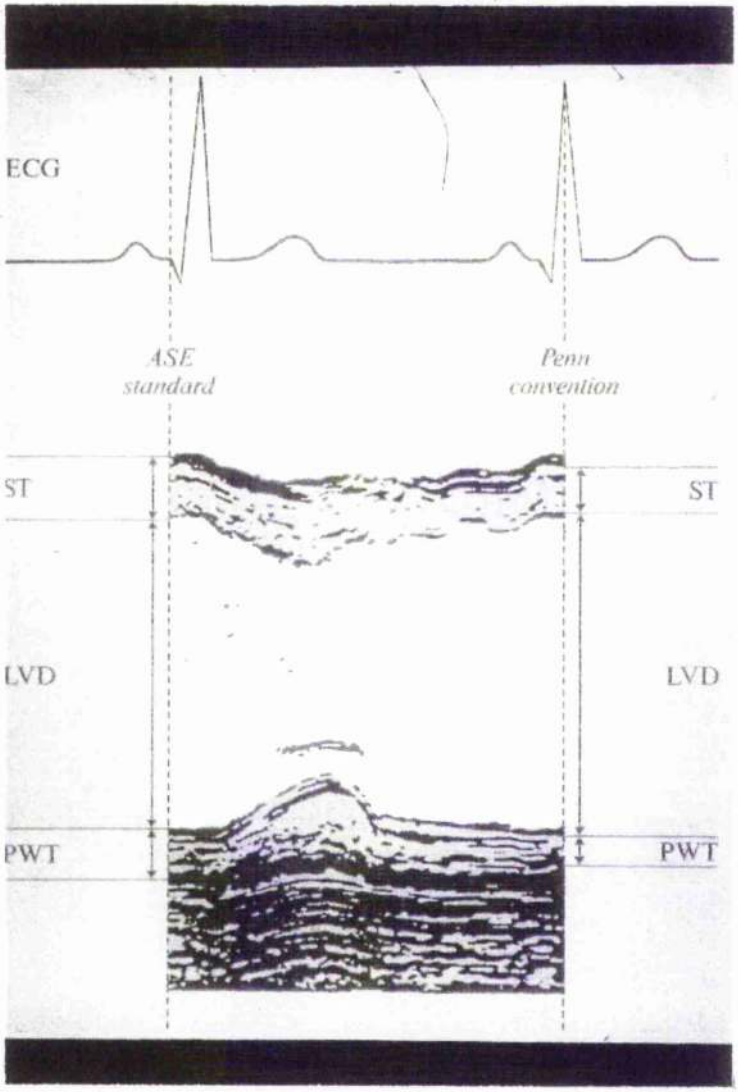

Figure 8

Penn convention measurements used to determine left ventricular mass according to the method of Devereux and Reichek

$LVID_p$ = left ventricular diastolic internal diameter according to Penn

PWT_p = left ventricular diastolic posterior wall thickness according to Penn

$IVST_p$ = thickness of the interventriclar septum in diastole according to Penn

These measurements were made over three consecutive cardiac cycles and the mean values calculated. Left ventricular mass was related to body surface area and expressed as the left ventricular mass index (90).

Devereux and Reichek's original validation was undertaken in 34 terminally ill patients with a variety of problems, the majority of whom had left ventricular cavities of normal dimensions (51). Four were reported to have renal failure, and analyses of clinical subgroups still showed the method to be accurate.(for further discussion see page 81).

The value of two electrocardiographic methods for the diagnosis of left ventricular hypertrophy was assessed in a dialysis population. Gubner and Ungerleider, through a comparison of hypertensive and non-hypertensive patients' electrocardiographs in 1942, considered LVH to be present if the sum of the R wave in lead I and the S wave in lead III exceeded 25mm (337). In 1949 Sokolov and Lyon defined a set of criteria using which distinguished patients with hypertension. aortic valve disease or coarctation of the aorta and presumed LVH from normal subjects (338). These were later subjected to a post-mortem validation by Allenstein and Mori when it was found that the QRS voltage changes amongst the criteria they originally described were the most sensitive and reliable indicators of the presence of LVH (339). These comprised the sum of the R wave in V5 and the S wave in lead V1 exceeding 35mm.

5.3.4 Left ventricular volume

In view of a predisposition of dialysis patients (most of whom are anuric or oliguric) to volume overload, particularly in the period immediately preceeding dialysis, left ventricular volume was assessed at both end-diastole and end-systole according to the method described by Tortoledo (340). The technique has been shown to correlate well with biplane angiographic measurements and involves measuring two diameters in the parasternal long axis view (figure 9) and three diameters and a long axis in an apical four chamber view (figure 10) at end-diastole. The measurements are repeated at end-systole (figure 11) and from a derived formula, previously validated by Tortoledo et al (340) which determines ejection fraction and hence stroke volume (SV=end-diastolic volume (EDV) x ejection fraction), the end-systolic volume (ESV) can be derived (ESV=EDV-SV).

5.3.5 Normal ranges

Normal ranges for echocardiographic measurements have been defined through the study of large populations of people of differing ages with good health and normal blood pressure (341). To repeat such large studies would be an unecessary and time consuming task and therefore predetermined normal ranges have been accepted (Appendix 3).

5.3.6 Reproducibility of echocardiographic measurements

The reproducibilty of echocardiographic left ventricular measurements in a single subject was calculated by measuring left

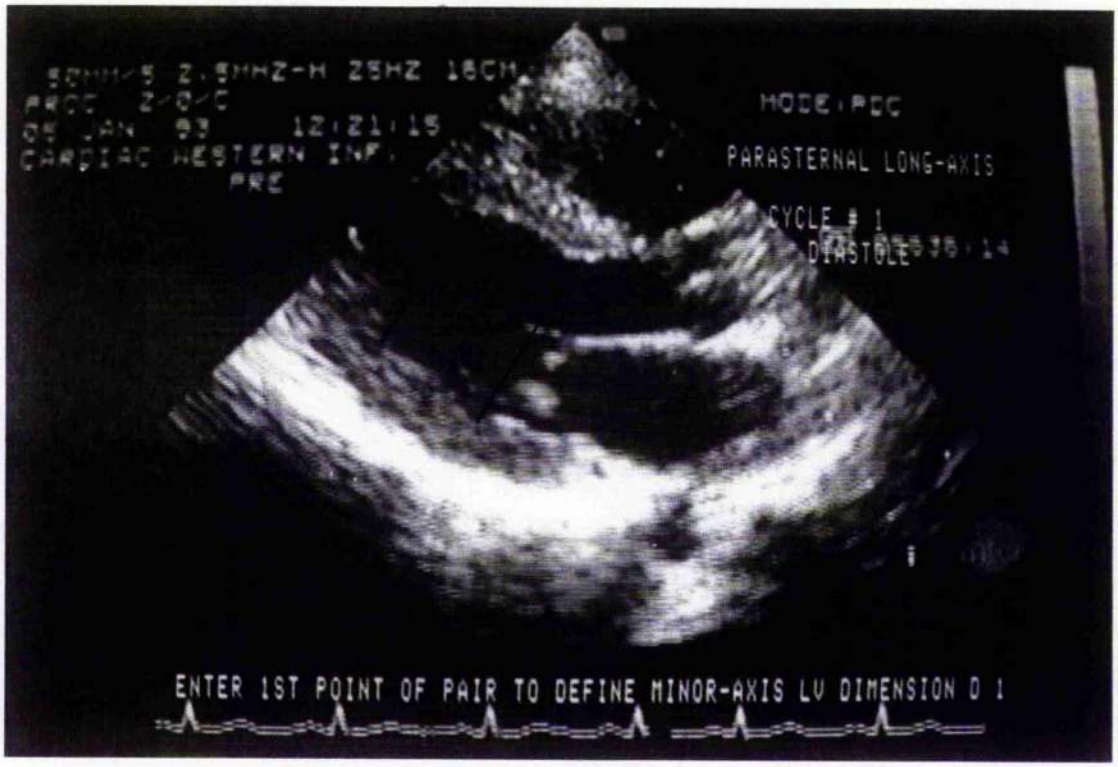

Figure 9

Left parasternal long axis view of left ventricle for determining end-diastolic volume - Tortoledo method

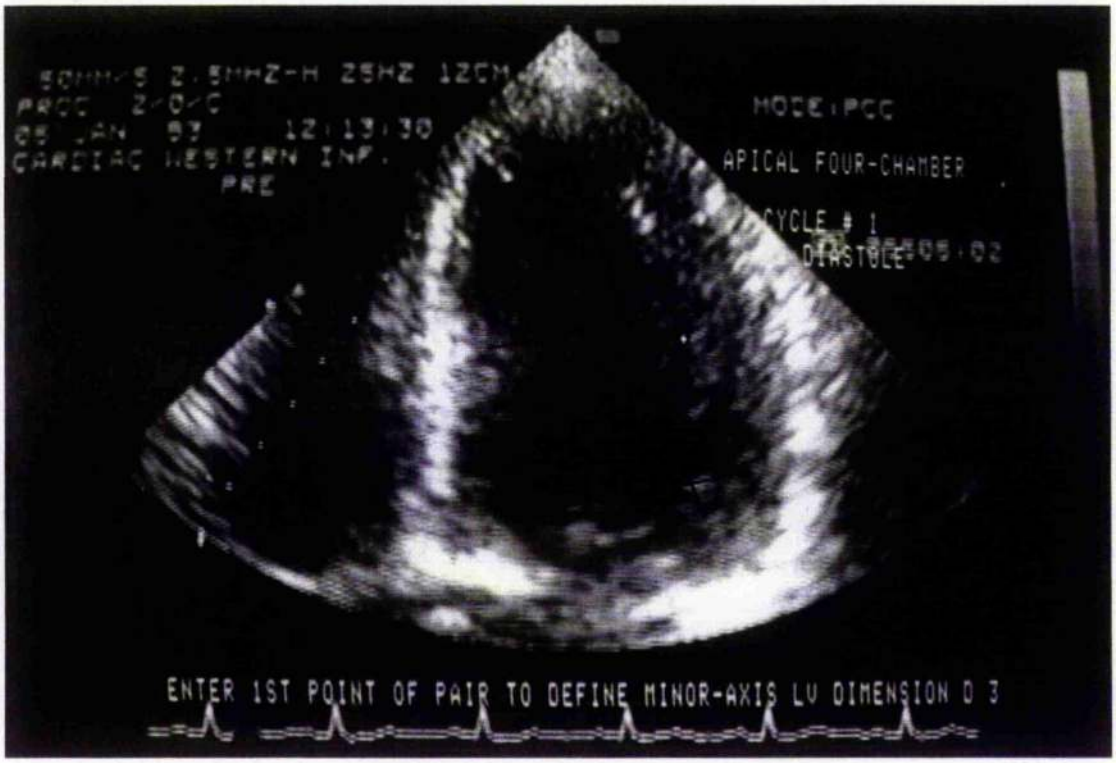

Figure 10

Apical four chamber view of left ventricle in diastole for determining end-diastolic volume - Tortoledo method

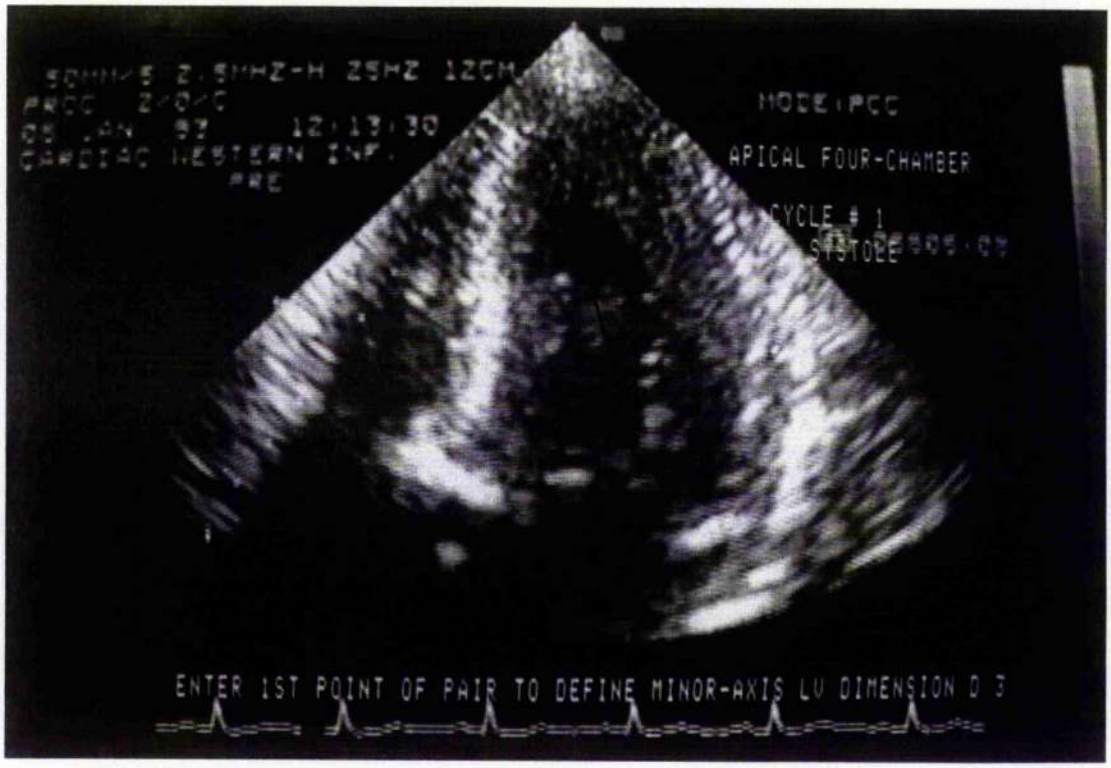

Figure 11

Apical four chamber view in systole for determining end-systolic volume - Tortoledo method

ventricular dimensions and volume in a healthy 21 year old volunteer on ten different occasions over ten days. The coefficient of variation was found to be 4.9% with respect to mass (51) and 4.3% with respect to end-diastolic volume (340). The author also repeated left ventricular measurements on the same M-mode echocardiogram on ten different occasions with an acceptable intra-observer coefficient of variation of 1.9%. A second echocardiographer with experience of determining left ventricular mass, but unaware of the nature of the scans, repeated measuremnts in eleven pre- and post-treatment echocardiograms, achieving a correlation of 0.98.

Section 4 Patients

Details of the patients who participated in the studies are given in appendix 4

Section 5 Statistical analyses

For comparison of paired data the students paired *t* test was used for normally distributed data and the paired Wilcoxon test for non-parametric data. For non-paired data which were not normally distributed, the Mann-Whitney test was applied. All results are given as 95% confidence intervals (95%CI) and p values, unless clearly not significant (ns).

Conditional logistic regression analyses were performed to look at factors which at the outset of renal transplantation might be related to

ventricular size. The Cox's proportional hazards method was used to assess these factors in relation to patient survival.

5.3.3 Left ventricular mass (continued)

Serial M-mode measurements may be flawed if patient or transducer position are not accurately reproduced. Two-dimensional echocardiography provides a guide to the left ventricle and helps to reduce angulation error, but may not improve results of experienced M-mode operators (90).

Several investigators have suggested that techniques relying on two-dimensional echocardiography alone give superior estimations of left ventricular mass (351, 352). These involve tracing the endocardial and epicardial surfaces of the left ventricle on stored, preferably diastolic images then applying formulae derived from geometric models of the left ventricle.

However such planimetric two-dimensional methods are still limited by poor image resolution and are inaccurate in cases where ventricular anatomy is distorted. Their main advantage is that they take account of the important influence of cavity volume on left ventricular mass determination (353).

Three dimensional reconstruction techniques may overcome many of these problems in the future (354).

Chapter 6

THE LEFT VENTRICLE IN A DIALYSIS POPULATION

In the course of investigating the effects of renal transplantation, erythropoietin treatment and parathyroidectomy on the echocardiographic appearances of the myocardium, 378 echocardiograms from 223 patients receiving regular renal replacement therapy were recorded. However the original intention to treat was not fulfilled in 14 cases for a variety of reasons such as unsuitable organ for transplantation, positive crossmatch, or revision of proposed therapeutic approach. In addition 20 random examinations of stable haemodialysis and CAPD patients were performed and together these echoes constituted the "dialysis only" group.

In all there were 220 "baseline" echoes from 217 dialysis patients (table 2). Despite selection for renal transplantation, erythropoietin therapy or sub-total parathyroidectomy, these people formed a representative sample of the local dialysis population most of whom were potential transplant recipients. A minority of patients would not receive a renal allograft on the grounds of advanced age, co-existant disease or a high degree of sensitisation.

By performing a cross-sectional comparison, the influence on the left ventricular echocardiographic appearances of sex, age, renal disease, hypertension, ischaemic heart disease, smoking habit and dialysis type and duration was examined.

TYPE OF ECHO	NUMBER	(* %)
Pre-transplant	153	(19 12)
Pre-erythropoietin	20	(1 5)
Pre-parathyroidectomy	10	(2 20)
Dialysis only	34	(2 6)
TOTAL	**217**	(24 11)

Table 2 Baseline echoes in dialysis patients
(* - % echoes of insuffient clarity to fully analyse)

Section 1

Sex, age, and the left ventricle

Of the 217 dialysis patients, 128 were male and 89 were female. Their mean ages were comparable (table 3) as were their blood pressures. However more of the men had a history of hypertension and as a group were taking significantly more antihypertensive medications than the women. As might be expected fewer women had a past history of cardiac disease and women had slightly lower haemoglobin concentrations.

The left ventricles in men were larger than in women (table 4). The interventricular septal thickness and end-diastolic dimension were significantly greater and consequently the derived left ventricular mass was also

	MALE	FEMALE
NUMBER	128	89
mean **AGE** (range)	39.8 (18-69)	41.9 (15-68)
BSA m^2 (mean±SD)	1.81±0.21	1.61±0.20
SBP (mean±SD)	147±21	144±22
DBP (mean±SD)	88±13	86±12
PREV. HT	105 (82%)	64 (72%)
BP drugs(median)	1	0*
Hb (mean±SD)	9.2±3.7	8.7±1.9
PTH (pmols/l)	38±56	41±47
CARDIAC history	31 (24%)	13 (15%)

Table 3 Characteristics of male and female dialysis patients

* (0.002 - 1.001) p=0.0013

median	*	MALE	FEMALE	95%C1 p
IVSTcm	27	1.6	1.5	(0.02 - 0.30) p=0.014
PWTcm	27	1.0	0.9	(0.00 - 0.16) p=0.09
EDDcm	27	5.5	4.7	(0.41 - 0.93) p<0.001
LVMIg/m^2	27	172	127	(21.4 - 56.9) p<0.001
EDVml	57	152	105	(28 - 55) p<0.001

Table 4 Left ventricular dimensions of male and female dialysis patients
* - number of missing values - applies in later whole group analyses unless stated otherwise

greater. However, even allowing for the increased body surface areas of the men (as reflected by the left ventricular mass indices), there was still a significant difference between male and female left ventricular mass. The end-diastolic volumes of the men also appeared disproportionately increased.

6.1.2 Age

Left ventricular measurements of the 217 dialysis subjects were examined and found to have a tendency to increase with age (table 5).

AGE	<20	20-29	30-39	40-49	50-59	60-69
Number	12	49	45	49	44	18
Male %	50	61	71	53	59	44
HT %	35	71	84	84	80	8
IVSTcm	1.4	1.5	1.6	1.5	1.7	1.6
PWTcm	0.9	1.0	1.1	1.0	1.0	1.1
EDDcm	4.8	5.2	5.0	5.3	5.3	5.2
LVMIg/m^2	117	141	169	155	176	175
EDVml	151	123	137	126	136	131

Table 5 LV dimensions and details of sex and hypertension according to age

There was also a trend for the prevalence of hypertension requiring medical therapy to increase with age, but the proportion of males (who might have been expected to have larger ventricles) was lower in the older age groups.

Section 2

Renal disease and the left ventricle

The causes of renal failure in the 217 dialysis patients were representative of the commonly reported causes of ESRD (3): glomerulonephritis was the most frequent underlying pathology in 31%, 9% patients had type I diabetes mellitus and in 6.5% patients who presented late with small kidneys, the cause was unclear. There was a slight excess (22%) of patients with reflux nephropathy or pyelonephritis. Left ventricular size varied, according to the primary renal disease (table 6). The lowest median left ventricular mass index was seen in the group with ESRF of uncertain cause and the fewest hypertensive patients, while the highest median LVMI was in patients with renovascular disease, all but one of whom had been treated for hypertension.

Renal disease	No.pts (%HT)	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
Unknown	14 (57)	141	1.6	1.0	4.7	136
APKD	19 (89)	145	1.7	0.9	4.5	108
Reflux / PN	48 (66)	147	1.5	1.0	5.2	125
GN	68 (82)	150	1.6	1.0	5.4	144
DM type I	19 (84)	153	1.6	1.1	4.9	115
RV	14 (92)	210	2.0	1.0	5.1	112

Table 6 LV dimensions and renal disease - median values given

(APKD - adult polycystic kidney disease, PN - pyelonephritis, GN- glomerulonephritis, DM - diabetes mellitus, RV - renovascular %HT - percentage of patients with history of hypertension)

6.2.2 Hypertension

The variation of LVMI with type of renal disease suggested hypertension might be responsible. A comparison of LV dimensions of patients with a history of hypertension requiring treatment,patients with previous malignant phase hypertension (grade 3 or 4 retinal changes), or those with no need for antihypertensive medication (table 7), confirmed an association not only between hypertension and increased LV mass but also between severe hypertension and marked left ventricular hypertrophy.

	Pt No	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
No HT	48	130	1.5	0.9	4.8	122
Hypertension	169	167*	1.6	1.0	5.3	136
(Malignant)	12	230	2.1	0.9	4.8	114

Table 7 Median LV dimensions and hypertension (HT)

* Difference between median non-hypertensive and hypertensive LVMI (14.45 - 55.69), p=0.001

6.2.3 Previous myocardial infarction (MI)

	Pt No	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
No MI	207	151	1.6	1.0	5.2	130
Previous MI	10	176	1.7	0.8	5.9*	158$

Table 8 Median LV dimensions and previous MI

* 95%CI (0.3 - 1.4), p=0.0037

$ 95%CI (-73 - -0.0), p=0.057)

Although the median LVMI of the 10 dialysis patients who had suffered a previous myocardial infarction was greater than those of patients with no history of myocardial infarction (table 8), this difference was not statistically significant. However the group of MI patients was small and the possibility that LVH predisposed to MI cannot be discounted. Increased susceptability to ischaemic injury through relative lack of blood supply is well recognised in other patients with cardiac hypertrophy (60,140)

In contrast following MI patients had a significantly greater end-

diastolic dimension, and a tendency to have a larger end-diastolic volume most likely as a consequence of ventricular damage and dilatation.

6.2.4 Smoking and LV dimensions

	Pt No	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
Non-smokers	115	148	1.6	1.0	5.1	123
Current+exsmokers	102	167	1.6	1.0	5.3	143
Current smokers only	70	172	1.6	1.0	5.3	136

Table 9 LV dimensions and smoking habit

Although both LV mass and LV end-diastolic diameter were slightly greater in the smoking compared to the non-smoking groups these differences were not significant (table 9).

Section 3 Dialysis and LV dimensions

At the time of the first dialysis echo, 129 patients were receiving haemodialysis and 88 patients CAPD. LV size did not vary with the method of dialysis employed (table 10).

	Pt No	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
Haemodialysis	88	154	1.6	1.0	5.2	126
CAPD	129	155	1.6	1.0	5.2	135

Table 10 Median LV dimensions of haemodialysis and CAPD patients

6.3.2 Duration of renal replacement therapy (RRT)

Months of RRT	Pt no	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
<3	15	161	1.75	1.07	5.55	201
3-5	10	137	1.51	1.09	4.75	109
6-12	30	135	1.50	1.05	5.20	127
13-24	38	143	1.59	1.00	5.20	137
25-36	26	125	1.50	0.90	5.30	165
37-60	28	170	1.62	1.00	5.30	143
61-84	32	167	1.60	0.90	5.40	118
84-120	14	129	1.65	0.93	4.40	106
>120	24	182	1.50	1.20	5.10	120

Table 11 Median LV dimensions and duration of renal replacement therapy

As there were no significant differences between CAPD and haemodialysis patients' ventricular size, the two groups were combined to perform a cross-sectional study on the effect of duration of dialysis on left

ventricular size (table 11). In reality many patients change from one mode of dialysis to another for medical or personal reasons or experience a period with a renal transplant interspersed. Of the 24 patients who had been receiving renal replacement tharapy for more than 10 years, only four had not been transplanted.

Table 11 data suggest a tendency for interventricular septal wall thickness, derived LV mass and end-diastolic volume to decrease within the first few months of dialysis. However the patient numbers were small and the observations did not reach statistical significance. Similarly the increased left ventricular mass index beyond 120 months of renal replacement therapy applied to a relatively small number of patients, but was significantly different from the median LVMI of patients on dialysis less than three years (table 12). Only the posterior wall thickness differed in the two groups.

Duration of RRT	Pt No	LVMI g/m^2	IVST cm	PWT cm	EDD cm	EDV ml
<36 months	119	142	1.52	1.00	5.20	138
>120 months	24	182*	1.50	1.20	5.10	120
*missing values		22	22	22	22	39

Table 12 Median LV dimensions of patients on renal replacement therapy for less than 3 years and more than 10 years.
*(-64.4 - -6.58), p=0.019

Excluding the 65 patients who had previously been transplanted resulted in a median LVMI of 159 g/m^2 for the remaining dialysis patients and did not significantly alter the findings.

Section 4 Serial echocardiography in dialysis patients

Of the 34 patients who had an initial "dialysis only" echo, 27 had a follow-up echocardiogram performed and 8 had a third. Seven did not have a second echo, because of death in 3 cases and transfer to another hospital in 4 cases

The interval between echoes was not constant and ranged from 7 to 99 weeks, with a mean value of 32 weeks. Two of the patients were commencing renal replacement therapy at the time of the first echo.

The characteristics of the dialysis patients with two echoes did not change between echoes (table 13). An example M-mode echocardiogram from a dialysis patient with marked LVH is shown (figure 12).

Although the median LV dimensions of the dialysis patients did not change with time (table 14), there was considerable individual variation in LVMI (figure 13), which could not be explained by the type of dialysis or the duration of treatment.

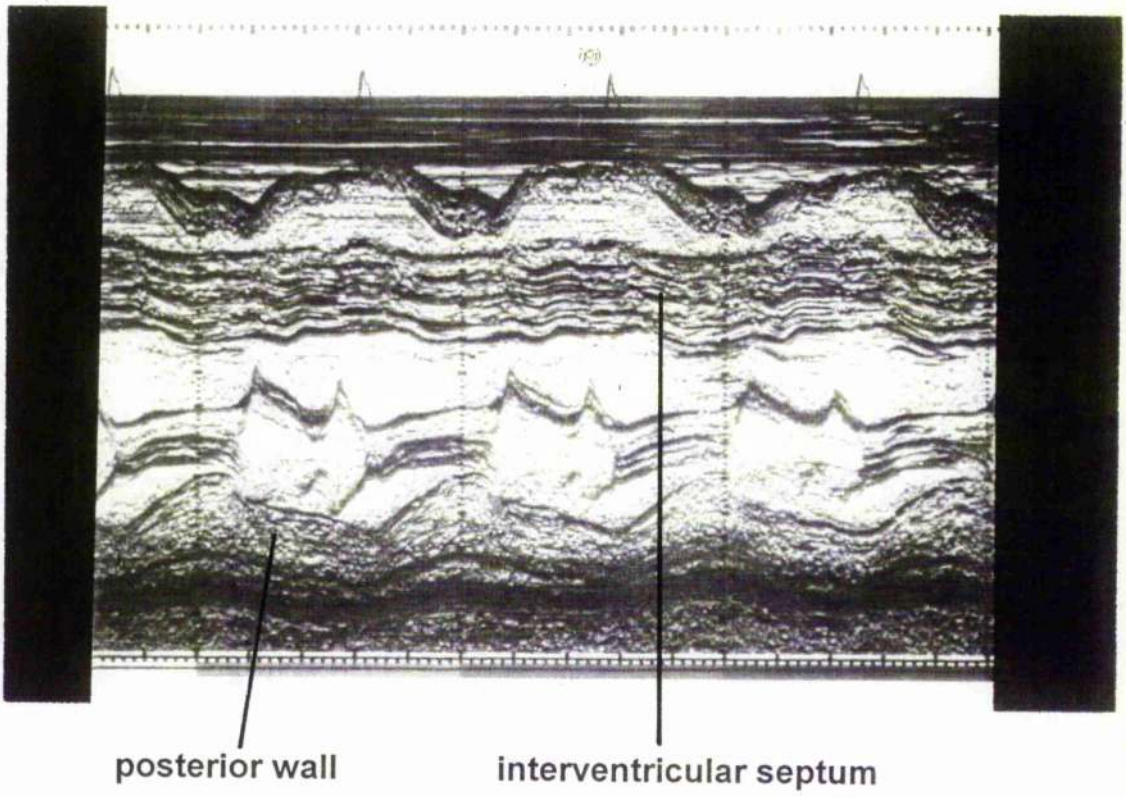

Figure 12

Pre-transplant M-mode echocardiogram showing marked thickening of the interventricular septum and posterior ventricular wall

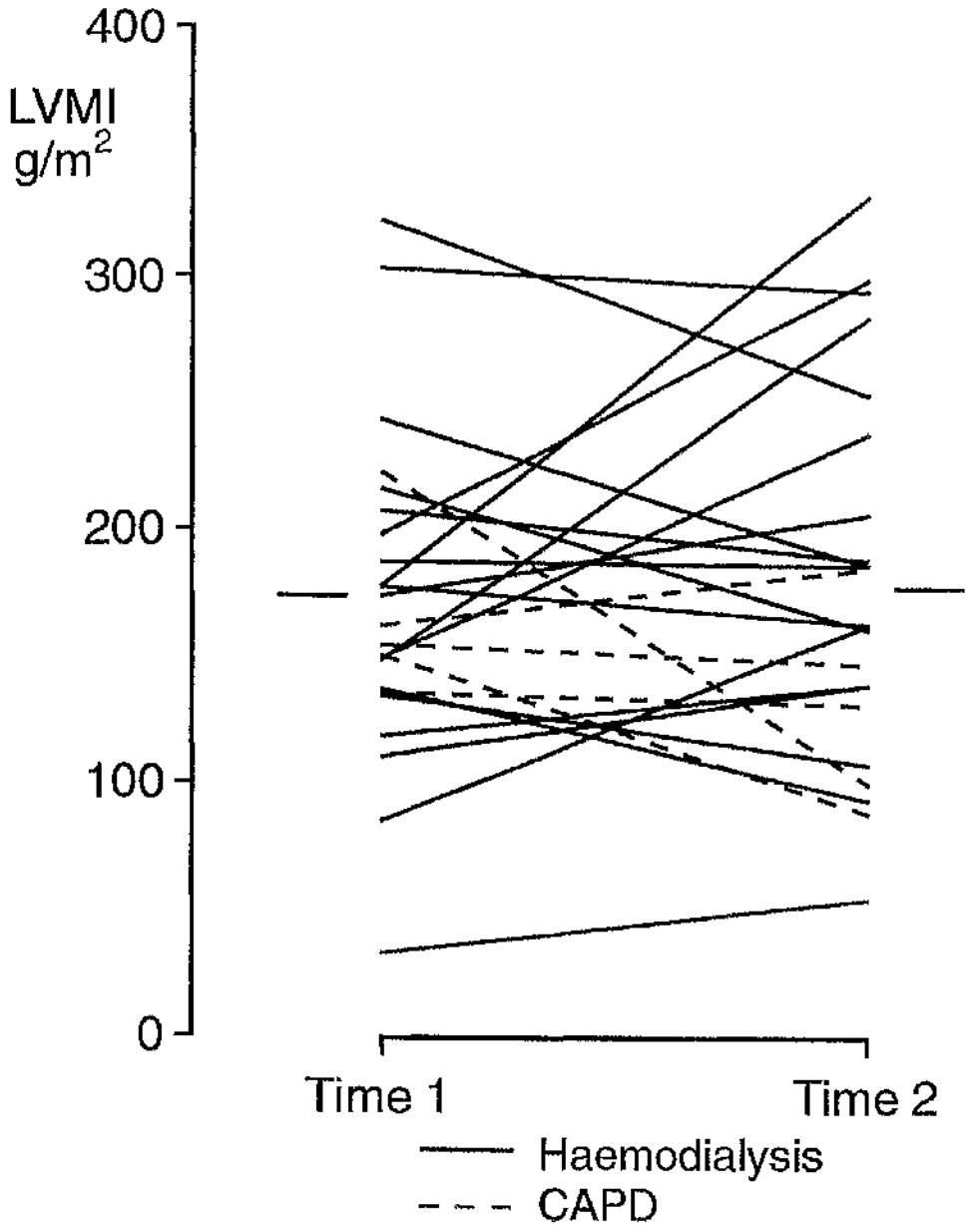

Figure 13

Left ventricular mass indices in patients receiving regular dialysis treatment (median values shown)

	TIME 1	TIME 2
BSA(mean±SD)	1.66±0.23	1.66±0.23
SBP (mean±SD)	144±20	145±27
DBP (mean±SD)	82±12	86±18
MBP (mean±SD)	101±19	106±19
BP drugs(median)	1.0	0
median **Hb** (g/dl)	8.1	8.2
median**PTH** (pmols/l)	32	16

Table 13 Serial dialysis echoes - patient characteristics

median	*	TIME 1	TIME 2
IVSTcm	3	1.6	1.5
PWTcm	3	1.1	1.0
EDDcm	3	5.2	5.1
LVMIg/m^2	2	175	162
EDVml	10	125	140

Table 14 Serial dialysis echoes - LV dimensions

Of the two patients beginning haemodialysis for the first time, one had a constant LVMI, while the other had an increase from 85 to 162g/m^2.

The LVMI's of 8 patients who had a total of 3 echo examinations are illustrated (figure 14) and show no discernible trend.

A moderately strong relationship between change in the mean of three systolic blood pressures and change in LVMI between the first two

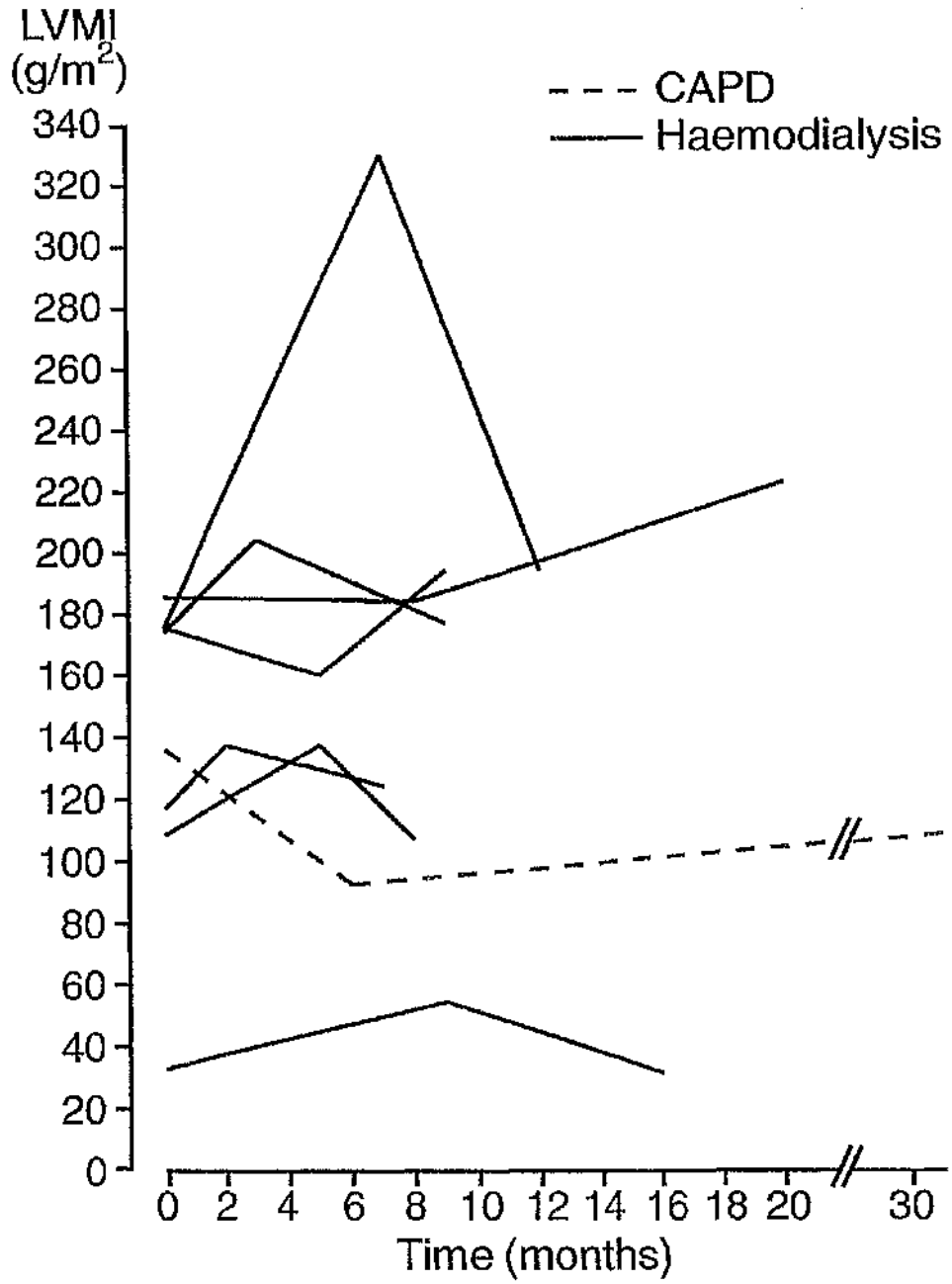

Figure 14

Left ventricular mass indices in 8 dialysis patients who had a series of three echocardiograms

echoes was evident, with a correlation coefficient of 0.585. Mean diastolic blood pressure and mean blood pressure on the day of echocardiography were less strongly correlated, with r values of 0.431 and 0.217 respectively.

There was also a correlation between change in haemoglobin and the change in LVMI between the two echocardiograms (figure 15).

Section 5 ECG and LV hypertrophy

Finally the utility of the electrocardiograph in diagnosing left ventricular hypertrophy in a dialysis population was examined.

Using two methods of determining the presence of LVH by voltage criteria, the Gubner Ungerleider (337) and the Sokolov Lyon technique (338), voltage scores were calculated and compared with the echocardiographically determined mass. An LVMI of greater than 109 g/m^2 for women and 134 g/m^2 for men was defined as hypertrophy (341).

One hundred and seventy-three satisfactory ECG tracings from the time of the echocardiogram were available for the dialysis group. The sensitivity and specificity of these two calculations of voltage criteria were calculated.

	GU LVH+	GU LVH-
ECHO LVH+	15	110
ECHO LVH-	2	46

Table 15 Gubner Ungerleider (GU) LVH versus echocardiographic LVH

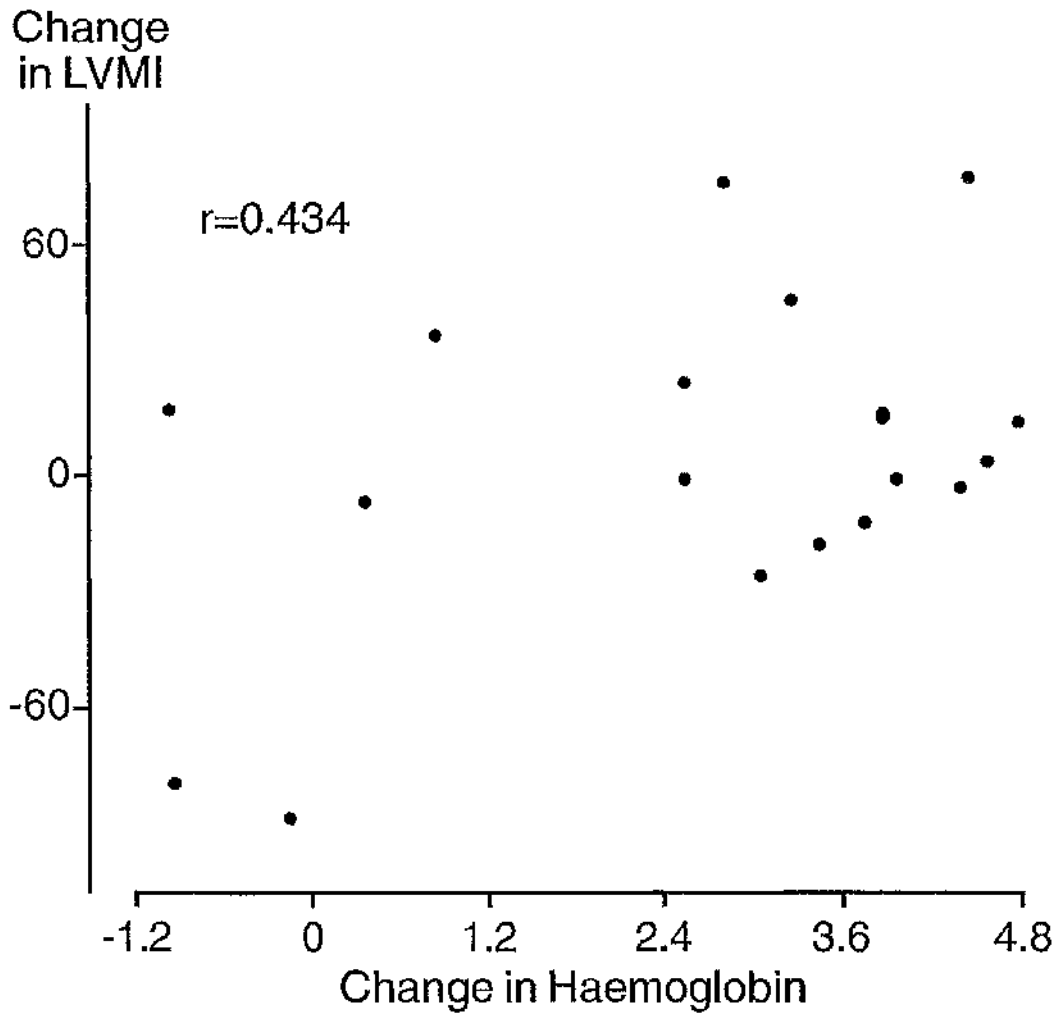

Figure 15

Correlation between change in haemoglobin and change in left ventricular mass index in regular dialysis patients

The Gubner-Ungerleider method of determining LVH was unlikely to identify the presence of LVH (sensitivity 12%), but was reasonably specific for the condition (specificity 95.8%).

	SL LVH+	SL LVH-
ECHO LVH+	61	64
ECHO LVH-	14	34

Table 16 Sokolov Lyon (SL) LVH versus echocardiographic LVH.

The Sokolov-Lyon method was only marginally better with frequent false negatives (64/125 - 51.2%) and a low sensitivity of only 48.8%. There were also a significant number of false negative results and the specificity was only 70.8%.

Section 6 Discussion

From this cross-sectional survey of a group of typical dialysis patients, it can be seen that two electrocardiographic techniques of assessing the presence of LVH by voltage criteria have a low sensitivity and fail to identify a significant proportion of patients with echocardiographic left ventricular hypertrophy. Of the 173 patients who had ECG's and satisfactory echoes concurrently, 72.2% had LVH by Framingham echo criteria (341). A similar proportion, (73.6%), of the 190 dialysis patients in whom echo mass could be determined had LVH.

These data indicate that the prevalence of LVH in this population of patients appears to be influenced by a number of factors. First, males have significantly greater left ventricular mass than females even allowing for their increased body surface area. This in part might be explained by a

higher prevalence of hypertension in men and possibly more severe hypertension, as judged by their requirement for a significantly greater number of anti-hypertensive drugs.

Whether hypertension, male sex or other factors predispose to the greater prevalence of cardiac disease amongst the male dialysis patients is not known. It is interesting that patients who had previously suffered a myocardial infarction had a significantly higher LV mass index than those who had not, the most likely explanantion being that LVH was acting as a cardiac risk factor. However the significantly greater end-diastolic dimension in the infarct group possibly distorted the determined LV mass because of influencing the cube formula.

Use of a "cut-off" LV mass to define the presence or absence of hypertrophy is questionable, as this study in common with others shows a tendency for LV mass to increase with age. The percentage of patients treated for hypertension also rises with age, thereby raising the question - is blood pressure alone responsible for the increasing prevalence of LVH?

The data on LV dimensions and renal disease would support such a role for hypertension as, with the exception of adult polycystic kidney disease only, the higher the percentage of patients suffering hypertension, the greater the LV mass. Left ventricular mass was highest in the small group of 14 patients with renovascular causes of renal failure, exactly half of whom had malignant phase hypertension.

Indeed the 12 patients in the total dialysis group who had a history of malignant hypertension had marked ventricular hypertrophy, particularly of the interventricular septum. This group was too small for the median LVMI's to be statistically different from the other hypertensive patients' LVMI's, but the median LVMI of hypertensive compared to non-hypertensive patients was significantly greater. These observations are in

accordance with published data on the influence of age. underlying renal disease and hypertension on cardiac hypertrophy, but without multiple logistic regression analyses it is impossible to attribute independent risk. As the patients sampled in this study were recruited for different purposes and did not represent the total dialysis population, this statistical method was not employed.

Animal experiments suggest arteriovenous shunts equivalent to dialysis fistulae can cause myocardial hypertrophy (293) through chronic volume overload. In humans, the lack of difference between ventricular dimensions of haemodialysis patients with vascular access and CAPD patients without, suggests the risk is small. This finding also contradicts studies which document a reduction in left ventricular mass with CAPD treatment (315,295).

In the cross-sectional survey the median LVMI was greater after many years of renal replacement therapy, but this observation was not supported by serial echocardiographic measurements in dialysis patients. While the LVMI varied considerably with time in individuals no trend was evident. This held true, irrespective of the type of dialysis. On the other hand, the change in systolic blood pressures, and to a lesser degree, the diastolic and mean blood pressures, correlated well with changes in left ventricular mass. There was also a relationship between change in haemoglobin and change in left ventricular mass index.

In summary, the cross-sectional study highlighted factors which might influence ventricular size, most notably blood pressure. The small serial study of dialysis patients, also suggested a correlation between change in blood pressure and change in LVMI and change in haemoglobin and LVMI. It was concluded that dialysis alone, as assessed in this project, did not have a predictable effect on left ventricular mass,

but that other factors, namely blood pressure and possibly haemoglobin were likely to be important.

Chapter 7

RENAL TRANSPLANTATION AND THE LEFT VENTRICLE

Several studies have shown that renal transplantation results in regression of left ventricular hypertrophy (295, 321, 322, 323, 324). However it is not clear whether this change relates to a reduction in blood pressure, amelioration of renal anaemia or resolution of hyperparathyroidism. The principle aim of this work was to compare changes in LV mass after transplantation with changes following erythropoietin therapy or parathyroidectomy, in order to ascertain the relative effects of each.

One hundred and fifty-three pre-transplant echoes were recorded, but post-transplant repeat echocardiography was only possible in 84 cases. Early graft failure (18 patients), patient death (11 cases), patient transfer (4 cases) and patient refusal to undergo further study accounted for the lack of follow-up in a majority of cases.

Echocardiography was repeated within 3 to 5 months in 64 patients, 6 to 11 months in 10 patients, 12 to 23 months in 8 patients and in 2 patients between 24 and 48 months.

One hundred and forty-two (93%) of the patients received cadaveric renal grafts and 11 underwent live donor renal transplantation, in one case unrelated. Fifteen patients had a series of three echoes.

Following renal transplantation the mean body mass index of the entire group of patients rose significantly (table 17). As might be expected, there was then a greater need for anti-hypertensive medication, but the resultant mean systolic and diastolic blood pressures were lower.

	PRE-TX	POST-TX	95%CI p
BMI mean±SD	1.76±0.22	1.81±0.21	(0.03-0.07) p<0.001
SBP median	149	137	(6.0-17.5) p<0.001
DBP mean±SD	90	85	(1.00-8.00) p=0.007
BP drugs mean±SD	0.67±0.85	1.25±0.92	(-0.87--0.35) p<0.001
Creatinine median	1110	140	(854-989) p<0.001
HB mean±SD	9.1±0.2	12.3±1.9	(2.6-3.7) p<0.001
PTHmedian(pmols/l)	18	7	(9.5-26.5) p<0.001

Table 17 Characteristics of patients before and after renal transplantation

With successful renal transplantation, serum creatinines fell, the mean haemoglobin rose and there was also a significant reduction in median parathyroid hormone concentration.

Changes in left ventricular dimensions were also observed with considerable variation in the left ventricular masses of the individual patients (figure 16), but no overall change in median LVMI (table 18).

This unexpected finding was associated with a tendency for both the median interventricular wall thickness and posterior wall thickness to increase. The end-diastolic dimension tended to decrease and there was a significant reduction in end-systolic dimension. However neither the end-diastolic nor end-systolic volume changed.

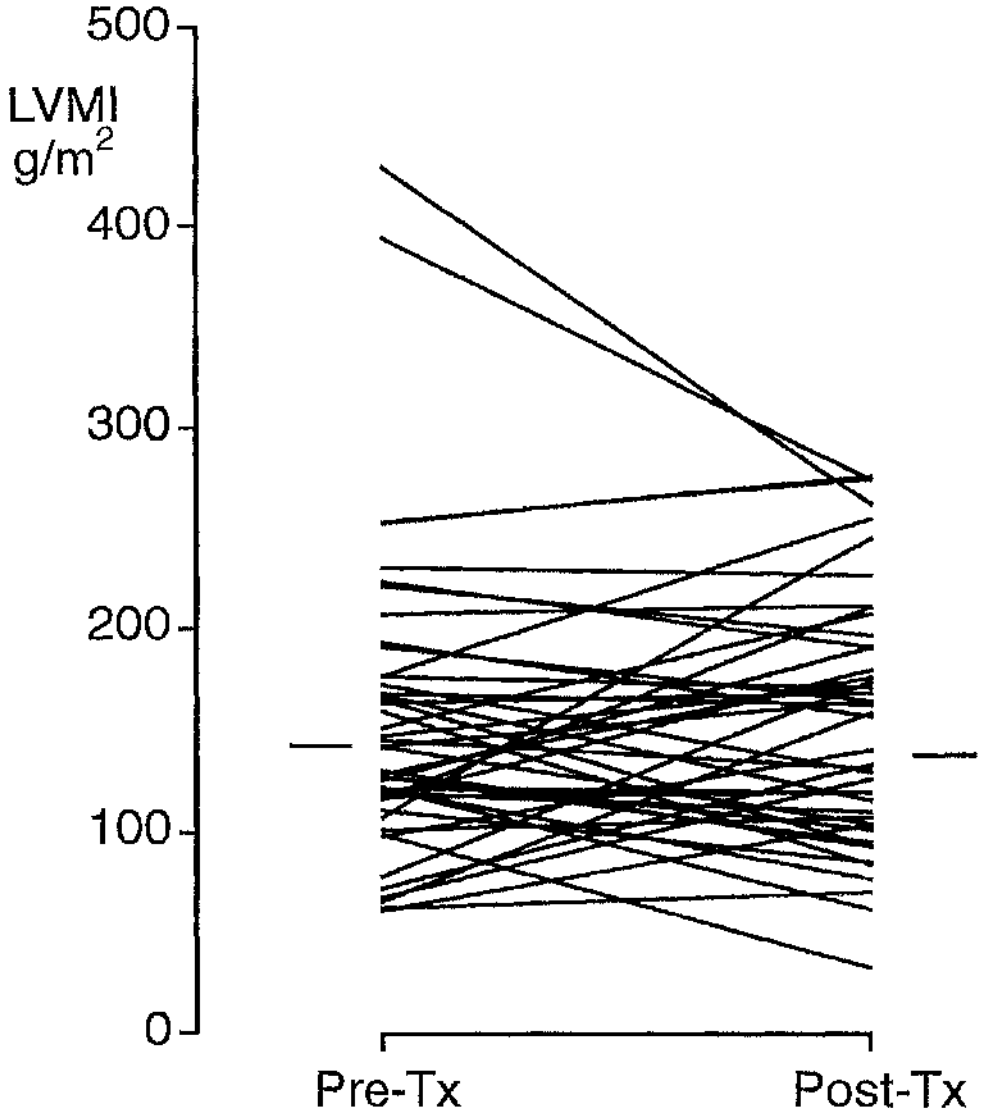

Figure 16

Left ventricular mass indices before and after renal transplantation (median values shown)

median	*	PRE-TX	POST-TX	95%CI p
IVSTcm	9	1.5	1.6	ns
PWTcm	9	1.0	1.0	ns
EDDcm	9	5.2	5.0	ns
ESDcm	9	3.7	3.3	(0.01-0.4) p=0.03
LVMIg/m^2	9	142	137	ns
EDVml	19	138	141	ns
ESVml	19	59	64	ns

Table 18 LV dimension before and after renal transplantation
* number of missing values - applies to later tables referring to whole group

The group of transplanted patients was divided according to the duration of the interval between the first and second echocardiograms, in case early changes in ventricular size were being masked (table 19).

INTERVAL months	**PT NO**	**PRE-TX LVMI**	**POST-TX LVMI**
<3	10	155	163
3-5	54	141	142
6-11	10	135	122
12-23	8	126	118
>23	2	154	98

Table 19 LVMI (g/m^2) after varying periods with a renal renal transplant

None of the wall thickness or LV cavity dimensions changed significantly for any of the intervals, though changes in the small group re-assessed for the second time beyond 23 months suggested regression of hypertrophy over the longer term. However this trend was not evident in the fifteen patients who went on to have a third echocardiogram (table 20).

median	*	Pre-tx	Post-tx 1	Post-tx 2
IVSTcm	2	1.6	1.7	1.6
PWTcm	2	1.0	1.0	1.1
EDDcm	2	4.8	5.1	5.3
ESDcm	2	3.1	3.2	3.1
LVMIg/m^2	2	143	137	137
EDVml	3	123	156	152
ESVml	3	49	68	59

Table 20 LV changes in pateints with 3 echocardiograms

For these patients the mean interval between first and the second echo was 5.5 months and the second and the third echo, 8.6 months.

Section 2

Misoprostol, a prostaglandin analogue and the LV

During the study period, the unit participated in a multicentre double-blind placebo controlled trial of the prostaglandin E_1 analogue, misoprostol (Searle). This was designed to determine whether

misoprostol prevented cyclosporin nephrotoxicity and acute graft rejection in newly transplanted patients. Experimental ischaemic renal injury is mitigated by prostaglandin analogues and in rats reversal of cyclosporin induced acute renal dysfunction has been described (342). A pilot study published in 1990 reported an encouraging and significant reduction in the incidence of acute rejection, but to the authors' surprise, an increased rather than decreased incidence of acute cyclosporin nephrotoxicity (343).

As the misoprostol trial had not been planned at the outset of the echocardiographic study and the drug was not known to have any cardiac effects, the protocol was not interupted. Between June 1989 and January 1990, 59 adults about to receive a renal transplant were enrolled and randomised to receive 100 micrograms (mcg), 200mcg, or placebo four times per day. Of these, 54 had pre-transplant echo examinations and 39 had follow-up scans. Patients continued on their trial drug for twelve weeks and their routine treatment was altered in no other way.The drug trial codes were not broken until the study was concluded in 1992, by which time it was evident that misoprostol had no significant effect on the incidence of either acute rejection or cyclosporin nephrotoxicity (344). At an investigators meeting a greater than expected incidence of cardiac arrhythmias and symptomatic myocardial ischaemia in misoprostol treated patients was reported, though not published.

The possibilty that misoprostol might be contributing to the lack of expected regression of LV hypertrophy was considered (table 21).

Misoprostol Patients	*	**200mcg** n=12		**100mcg** n=12		**placebo** n=13	
median		pre	post	pre	post	pre	post
IVSTcm	6	1.6	1.5	1.4	1.6	1.4	1.7
PWTcm	6	0.7	1.0	1.0	1.1	1.0	1.1
EDDcm	6	5.6	5.2	5.2	4.6	5.1	4.8
LVMIg/m^2	6	164	165	121	163	135	152
EDVml	8	149	133	140	113	144	148

Table 21 LV dimensions in the misoprostol study showing the high dose, low dose and placebo groups

No significant differences were identified between the treatment groups, although numbers were small. For these reasons the 100mcg and 200 mcg groups were combined and the changes which occured in LV size during misoprostol administration were compared to the LV changes in the placebo treated groups. Only the reduction in end-diastolic volume with misoprostol was found to be significant (-5.05 - 7.0) p=0.032. Changes in blood pressure, haemoglobin and PTH were comparable in the three groups.

As a trend for LVMI to increase was observed in the placebo group as well as the active treatment groups, misoprostol was unlikely to account for the contradictory findings. Since there were no striking changes with misoprostol it was not regarded as a factor which would confound other analyses.

Section 3

Dialysis and subsequent renal transplantation

In the survey of dialysis patients, there were no significant differences between the two groups' ventricular dimensions, suggesting again that arteriovenous fistulae do not predispose to left ventricular hypertrophy. However, could the presence of a fistula in a patient with a functioning renal transplant impede regression of ventricular hypertrophy? The effects of renal transplantation were therefore compared in those patients with functioning vessel access and those patients without.

median	HD pre	HD post	HD vs PD 95%CI p	PD pre	PD post
IVSTcm	1.5	1.4	ns	1.6	1.8
PWTcm	1.0	1.0	ns	0.9	1.0
EDDcm	5.2	5.2	(3.67-4.4) p<0.001	5.3	4.8
ESDcm	3.7	3.4	(-0.98--0.20)p=0.004	3.6	3.1
LVMIg/m^2	142	129	ns	141	160
EDVml	124	136	ns	141	141
ESVml	56	68	ns	60	62

Table 22 Changes in LV dimensions in haemodialysis patients with shunts (n=49) and CAPD patients without (n=35). Pre and post measurements in each of these groups were not statistically different. 95% CI and p values refer to the median changes of the HD group versus the PD group.

In haemodialysis patients with fistulae, the end-diastolic diameter following renal transplantation remained unchanged, compared to the end-diastolic diameter in CAPD patients without vessel access. The

magnitude of change in the end-systolic diameter was also greater in PD patients, implying that AV fistulae or other forms of vascular access are associated with ongoing dilatation of the ventricular cavity. End-diastolic and end-systolic volumes changed less, but in ways which supported this hypothesis.

As well as differing with respect to vascular access, haemodialysis patients tend to be more anaemic than CAPD patients because of inevitable blood loss and haemolysis associated with haemodialysis.

Section 4

Anaemia LV changes following transplantation

In fact the haemoglobins of the haemodialysis and CAPD patients were similar at the time of the first echo (9.2±2.0 and 8.9±1.8 respectively), perhaps in part reflecting the efficacy of erythropoietin therapy which 10% of the haemodialysis patients and 3% of the CAPD patients were receiving. The possibility that a higher pre-transplant haemoglobin might be reducing the magnitude of subsequent ventricular change was examined, by comparing patients with haemoglobins below 8g/dl and above 10 g/dl at the time of surgery.

HB median	*	<8g/dl pre	n=26 post	95%CI p	>10g/dl pre	n=29 post
IVSTcm	4	1.6	1.8	ns	1.6	1.5
PWTcm	4	0.9	1.0	ns	0.9	1.0
EDDcm	4	5.2	4.9	ns	5.3	5.2
ESDcm	4	3.6	3.2	ns	3.8	3.4
LVMIg/m^2	4	143	163	ns	123.	129
EDVml	10	143	139	ns	140	149
ESVml	10	72	63	ns	60.	69

Table 23 Comparison of ventricular response to renal transplantation in anaemic and less anaemic patients

The only significant change to occur in the anaemic patients (haemoglobin <8g/dl), was a decrease in the end-systolic dimension from 3.6 to 3.2cm (-0.8-- -0.125), p=0.009. None of the changes in the less anaemic group met with statistical significance.

A comparison of changes in the anaemic and less anaemic groups suggested that the end-diastolic diameter was less likely to diminish following renal transplanation with a higher haemoglobin. Perhaps as a consequence of less ventricular cavity dilatation, the ventricular walls in the anaemic patients were thicker post-operatively, but these observations did not hold up to statistical testing.

However a weak negative correlation between the change in haemoglobin and change in left ventricular mass index after renal transplantation was observed (figure 17)

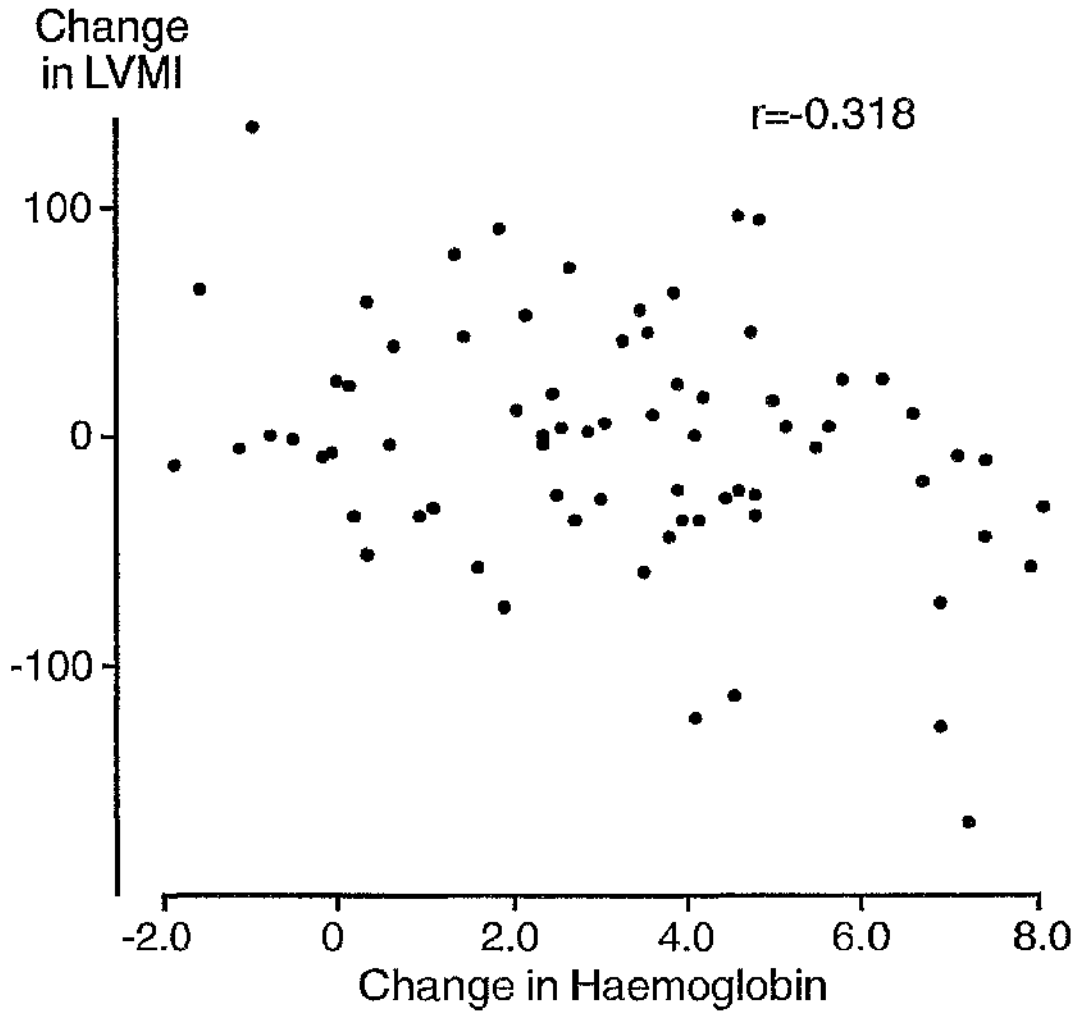

Figure 17

Correlation between change in haemoglobin and change in left ventricular mass index in transplanted patients

4.2 Viscosity, transplantation and the left ventricle

Blood viscosity is reported to have an independent effect on ventricular hypertrophy (107), and through its relationship with haematocrit might be predicted to change after renal transplantation. As these laboratory assays could be performed only during working weekday hours, not all of the 84 patients had a complete viscosity data-set (table 24).

median	*	Pre-tx	Post-tx	95% CI p
SBP		150	135	ns
DBP		90	85	ns
No BP drugs		1	2	ns
HB		8.4	12.8	(2.6-4.65) p=0.000
Whole BV	0	2.24	2.7	(0.195-0.795) p=0.02
Plasma V	0	1.34	1.29	ns
Corrected V	0	3.10	3.09	ns
Relative V	0	2.34	2.38	ns
IVSTcm	1	1.6	1.7	ns
PWTcm	1	1.0	1.0	ns
EDDcm	1	5.0	5.1	ns
LVMIg/m^2	1	130	140	ns

Table 24 Blood viscosity (BV) (mPa.s) changes after renal transplantation in 26 patients

The whole blood viscosity measured at high shear rates increased significantly after renal transplantation, to a median value within the

normal population range. As plasma viscosity and the corrected viscosity remained unchanged, the whole blood viscosity changes were presumed to be related to the rise in haematocrit, although increased red cell deformability could not be discounted. There was a weak correlation between change in whole blood viscosity and change in LV mass (r=-0.366).

Section 5

Renal transplant factors and ventricular change

If renal transplantation does genuinely result in a change in ventricular morphology, then the degree of change might be related to how well the renal allograft is functioning. Chronic rejection is the commonest cause of chronic renal dysfunction in transplant recipients, which in turn is related to the incidence of acute transplant rejection episodes. A patient with an elevated serum creatinine, anaemia, hyperparathyroidism and hypertension because of a failing transplant shares many of the problems of a dialysis patient, but in addition would be receiving immunosuppression.

Ventricular changes after renal transplantation were assessed in relation to the serum creatinine at the time of the post-transplant echocardiogram (table 25).

SERUM CREAT.	<120	<120	120 -200	120 -200	201- 1000	201- 1000
	pre	post	pre	post	pre	post
IVSTcm	1.5	1.3	1.5	1.5	1.7	1.7
PWTcm	0.9	1.0	1.0	1.0	1.0	1.0
EDDcm	4.7	4.8	5.2	5.1	5.9	5.5
ESDcm	3.2	3.2	3.7	3.2	4.1	3.6
LVMIg/m^2	116	119	149	138	160	168
EDVml	131	115	136	134	175	173
ESVml	84	63	60	55	100	74
Pt no	26		40		15	

Table 25 LV dimensions in relation to final serum creatinine (creat).

No significant differences were apparent in the three groups of patients who attained different levels of renal function. Similarly there was no correlation between the degree of post transplant proteinuria and change in left ventricular mass index.

Hypertension is a well recognised side-effect of cyclosporin, now the commonest immunosuppressive agent to be used after renal transplantation. At the time of the study cyclosporin was being used routinely in combination with prednisolone in all patients at least during the first year. Four patients with stable transplant function then elected to participate in a conversion trial involving changeover to an azathioprine and prednisolone regime.

A comparison of the cyclosporin and the four azathioprine treated patients (all of whom had initially received cyclosporin), revealed that

those taking azathioprine had a lower median BP (126/99 vs 137/85) on fewer antihypertensives (mean of 0.25 vs 1.3 drugs). The degree of change in LVMI in azathioprine and cyclosporin patients was identical, although patient number are small.

Section 6

Males and females

Figure 16 of individual patients' LVMI before and after renal transplantation, shows that patients with the highest and lowest LVMI's exhibited the greatest degree of change - suggesting regression towards the mean. Given that males in the dialysis population had higher LV masses than females, there was possibly greater potential for change in LVMI in men, but this was not confirmed (table 26).

	Male	n=50		**Female**	n=34
median	pre	post	95%CI p	pre	post
IVSTcm	1.6	1.6	ns	1.4	1.5
PWTcm	1.0	1.0	ns	0.9	0.9
EDDcm	5.3	5.2	ns	4.8	4.8
LVMIg/m^2	159	146	ns	118	126

Table 26 LV dimensions in transplanted men and women

Section 7

Patient outcome and LV changes after renal transplantation

Mortality from all causes, particularly cardiovascular disease, is high in transplanted patients (chapter 1). To determine whether patients who died had different cardiac characteristics, the changes after transplantation in the surviving transplant patients were compared to those in the non-survivors (table 27).

	Alive	n=73		Dead	n=11
median	pre	post	95%CI p	pre	post
IVSTcm	1.5	1.5	ns	1.5	1.8
PWTcm	1.0	1.0	ns	0.8	1.0
EDDcm	5.1	5.1	(-1.3--0.04) p=0.037	5.8	4.9
ESDcm	3.5	3.3	(-1.26--0.11) p=0.02	4.3	3.4
LVMIg/m^2	131	132	ns	159	169
EDVml	134	139	ns	143	138
ESVml	57	60	ns	63	77

Table 27 LV changes in survivors and non-survivors.

Patients who survived had very little change in either ventricular wall or cavity size after renal transplantation. Amongst those who died, the initial pre-transplant LV internal dimension was greater, though this did decrease subsequently. In the deceased group, both the interventricular septum, and posterior wall widths increased, perhaps as a consequence of the alleviation of ventricular stretch.

Section 8 Diastolic function after renal transplantation.

Diastolic function as assessed indirectly by the left atrial diameter and doppler transmitral flow, was markedly impaired as judged by the very low E:A ratios, and did not change significantly following renal transplantation (table 28).

median	*	PRE-TX	POST-TX	95%CI p
L atrial diam	29	41.3	42.2	ns
E:A ratio	45	0.88	0.96	ns

Table 28 Indices of diastolic function across renal transplantation

Nor was there any correlation between changes in E:A ratios and changes in LV mass.

Section 9
Patients whose LV mass decreased

The characteristics of 37 patients whose LV mass was lower at the time of the follow-up echo were no different from the rest of the transplant group. Furthermore the reduction in LV mass could not be attributed to change in any one constituent of the heart. In this subset of patients the blood pressures, need for antihypertensive medication and the haemoglobin and PTH changes, were indistinguishable from the other patients whose LV mass remained stable or increased.

Section 10

Risk factors for LV hypertrophy and death in transplanted patients

A number of different patient variables were examined by means of multiple logistic regression analyses to determine whether they were independently related to:-

a) the LVMI at the time of transplantation

b) subsequent patient outcome

The variables (table 29), as recorded on the day of renal transplantation were grouped according to whether they were well established as cardiovascular risk factors in dialysis populations (group 1), likely to be associated with LVH or death (group 2), or whether such an association was merely speculative (group 3). One-hundred and sixty three patients were included in the analysis on an "intention to treat" by transplantation basis.

The raw data were log transformed and using multivariate regression analysis for each group in turn, the Group 1 covariates SBP and EDV were found to be significantly associated with LVMI ($p=0.003$ for each). Applying the same model with group 2 variables, male sex was very significantly associated with LVMI and haemoglobin was of borderline significance allowing for the relatively small number of covariates. When the two groups were combined, the influence of end-diastolic volume was countered by haemoglobin. No group 3 variables were found to be significant in combination with the important group 1 and 2 variables. In the final analysis, SBP ($p=0.0002$) and sex ($p=0.002$) were significantly associated with LVMI, SBP most strongly.

GROUP 1	GROUP 2	GROUP 3
SBP	Sex	Alk. phophatase
DBP	Body mass index	Albumin
MBP	Number BP drugs	PTH
LVMI	Haemoglobin	Heart rate
Previous HT	Ca x PO4	IVST
Diabetes	E:A ratio	PWT
Smoking habit	Age at 1st dialysis	EDD
EDV	Age at death	ESD
Cholesterol	Family history	L atrial diameter
Triglyceride		MWT
Cardiac disease		RWT
		ESV
		Type of dialysis

Table 29 Groups of variables for regression analyses

In the multivariate analysis the true significance of haemoglobin in relation to LVMI was difficult to define because of its interaction with end-diastolic volume.

The second analysis involved looking at the grouped covariates in relation to outcome. Thirty of the original 163 patients died, and a survival analysis was performed according to the Cox's proportional hazards model. The only variable which was found to be significantly associated with outcome was the age at dialysis

Section 11

Discussion

Renal transplantation in this series resulted in restoration of renal function, resolution of anaemia and in most patients hyperparathyroidism, but not in the overall reduction in left ventricular mass which has been reported in other studies. The data were examined to determine whether this difference might be a explained by the length of the follow-up period, by the inclusion of 24 patients in a trial of the prostaglandin analogue misoprostol, by the continued presence of vascular access, by use of pre-transplant erythropoietin or by the level of renal transplant function attained. None of these factors was found to have a clear or significant influence on the lack of change in median left ventricular mass.

Nevertheless, many patients did exhibit a significant individual change in LV mass as measured by the validated echocardiographic technique, prompting the question - what might be responsible? Comparison of patients whose myocardial mass decreased and stayed static or increased, provided no clues.

A number of interesting points did emerge: despite no overall change in LV mass for the group, there was a tendency for the ventricular wall thickness to increase and the cavity size at end- diastole and systole to be smaller in the post-transplant period. This did not apply to patients with vessel access, in whom there was a suggestion of persisting LV cavity dilatation. On the other hand patients with the most severe anaemia pre-operatively tended to experience the greatest reduction in end-diastolic diameter. There was also a negative correlation between change in haemoglobin and change in LV mass.

Whole blood viscosity increased significantly following renal transplantation (in parallel with the rising haematocrit) but there was no associated change in ventricular mass.

The patients who died in the early years following renal transplanation, had larger ventricular cavities at the time of surgery, possibly reflecting previous myocardial damage. However, multivariate analysis did not show cavity dilatation to be a significant factor. Only age at start of dialysis was associated with subsequent survival.

Male sex and elevated systolic blood pressure at the time of transplantation were found to be independent determinants of left ventricular mass index. The influence of haemoglobin was less conclusive, but of possible importance.

Chapter 8

ANAEMIA AND THE LEFT VENTRICLE

There is a wealth of experimental evidence to point to the stressful effects of anaemia on the myocardium (chapter 3). However, until recently, the only successful method of treating the chronic anaemia of human renal failure was by blood transfusion which carried risks of infection and sensitisation to HLA antigens, caused a degree of volume loading and was merely of short term benefit. The advent of recombinant human erythropoietin was therefore met with considerable clinical and scientific interest. The drug first became available in Glasgow for trial use late in 1988, at which time studies of its effects on cardiovascular function were awaited. Erythropoietin, or epoietin by its generic name, gained its product licence in 1990 and is now in widespread use.

A small early supply of erythropoietin provided an opportunuty to study the cardiac effects of correcting anaemia and to compare these with the ventricular response to a rise in haemoglobin which occurs following successful renal transplantation.

Section 1 Dialysis, anaemia and the left ventricle

To begin with, an exploratory survey of how anemia appears to affect the left ventricle in dialysis patients was undertaken (table 30).

median	Hb<6 n=12	Hb6-7.9 n=68	Hb 8-10 n=74	Hb>10 n=63
SBP	146	146	145	144
DBP	87	88	89	88
BP drugsmean	0.3	0.90	1.15	0.58
PTHpmols/l	30	20	27	16
IVSTcm	1.9	1.6	1.5	1.6
PWTcm	1.0	1.0	1.0	1.0
EDDcm	5.2	5.3	5.0	5.2
ESDcm	3.5	3.7	3.4	3.5
LVMIg/m^2	194	168	146	150
EDVml	160	122	123	142
ESVml	76	61	55	65
E:A ratio	1.03	0.91	0.86	0.84

Table 30 LV dimensions and different degrees of anemia in the dialysis population

This suggested that the interventricular septal thickness, the LV mass and the end-diastolic volume were all greater in patients with severe anaemia (haemoglobin less than 6g/dl) compared to those with haemoglobins of 6-8g/dl. These still significantly anaemic patients in turn had a higher median LV mass than those with haemoglobins between 8 and 10g/dl. Above a haemoglobin level of 10 g/dl there was no further change. It is also noteworthy that with falling LV mass, the E:A ratio also rose progressively and possibly paradoxically, though remained low. Severe anaemia associated with LVH might be expected to result in a lower E:A ratio signifying impaired ventricular diastolic filling.

Section 2 The ventricular effects of erythropoietin treatment

With the introduction of erythropoietin it was possible to study the correction of anaemia and any associated cardiac effects. Twenty patients had echocardiograms at the beginning of erythropoietin therapy. As treatment had to be dicontinued early in one patient because of transient visual loss and another was transplanted. there were follow-up echoes in 18 patients after a mean interval of 16.5 weeks. Eleven patients were stablished on haemodialysis,6 on CAPD and one had a failing renal transplant.. There were 11 men and 7 women.

Six of the 18 patients were treated with 50 units/kg of erythropoietin (epoietin alfa, Cilag-Biotech) intravenously three times per week after dialysis for the first twelve weeks of treatment, as part of a clinical trial of the drug. Thereafter they received a median dose of 2000 units of epoietin beta, (Bohringer) subcutaneously three times per week, in common with the other non-trial patients. One man experienced transient visual loss and discontinued treatment, another required admission with uncontrolled hypertension which responded to temporary drug withdrawal for 4 days and an increase in antihypertensive medication.

The majority of patients reported benefit within a few weeks of starting therapy - improved effort capacity, better appetite, and a generally increased sense of well being. In 5 patients, objective exercise testing demonstrated prolongation of exercise time and improved oxygen uptake at maximal exercise. In one case exercise induced ST segment depression on ECG disappeared after erythropoietin treatment.

	PRE-EPO	POST-EPO	95% CI p
BSA mean±SD	1.67±023	1.67±0.24	ns
SBP median	143	143	ns
DBP median	83	87	ns
BPdrugs mean±SD	0.94±1.08	1.47±1.3	(-0.12-0.94) p=0.015
Hb median	6.8	10.0	(1.65-3.75) p=0.001
PTH pmols/l	11.5	16	ns
CA x PO4	5.01	4.7	ns

Table 31 Response to erythropoietin - all patients

A significant rise in haemoglobin was seen with erythropoietin therapy (table 31). The median blood pressure did not change, but this was only achieved by the prescription of an increased number of anti-hypertensive drugs.

median	*	PRE-EPO	POST-EPO	95%CI p
IVSTcm	0	1.61	1.6	ns
PWTcm	0	1.0	1.0	ns
EDDcm	0	5.4	5.5	ns
ESDcm	0	3.6	3.6	ns
LVMIg/m^2	0	183	179	ns
EDVml	6	162	176	ns
ESVml	6	75	92	(-93 - -44) p=0.04
E:A	2	1.11	0.98	ns

Table 32 LV dimensions of all erythropoietin treated patients (n=18)

The only significant change to occur in LV dimensions with erythropoietin treatment was an increase in end-systolic volume (table32). However, lack of change in median LV mass did not signify lack of change in individual patients (figure 18). This shows that LVMI fell in patients who responded to erythropoietin, but increased markedly in the two patients who did not respond to treatment.

The characteristics of the erythropoietin responders (table 33), were no different from the group as a whole.

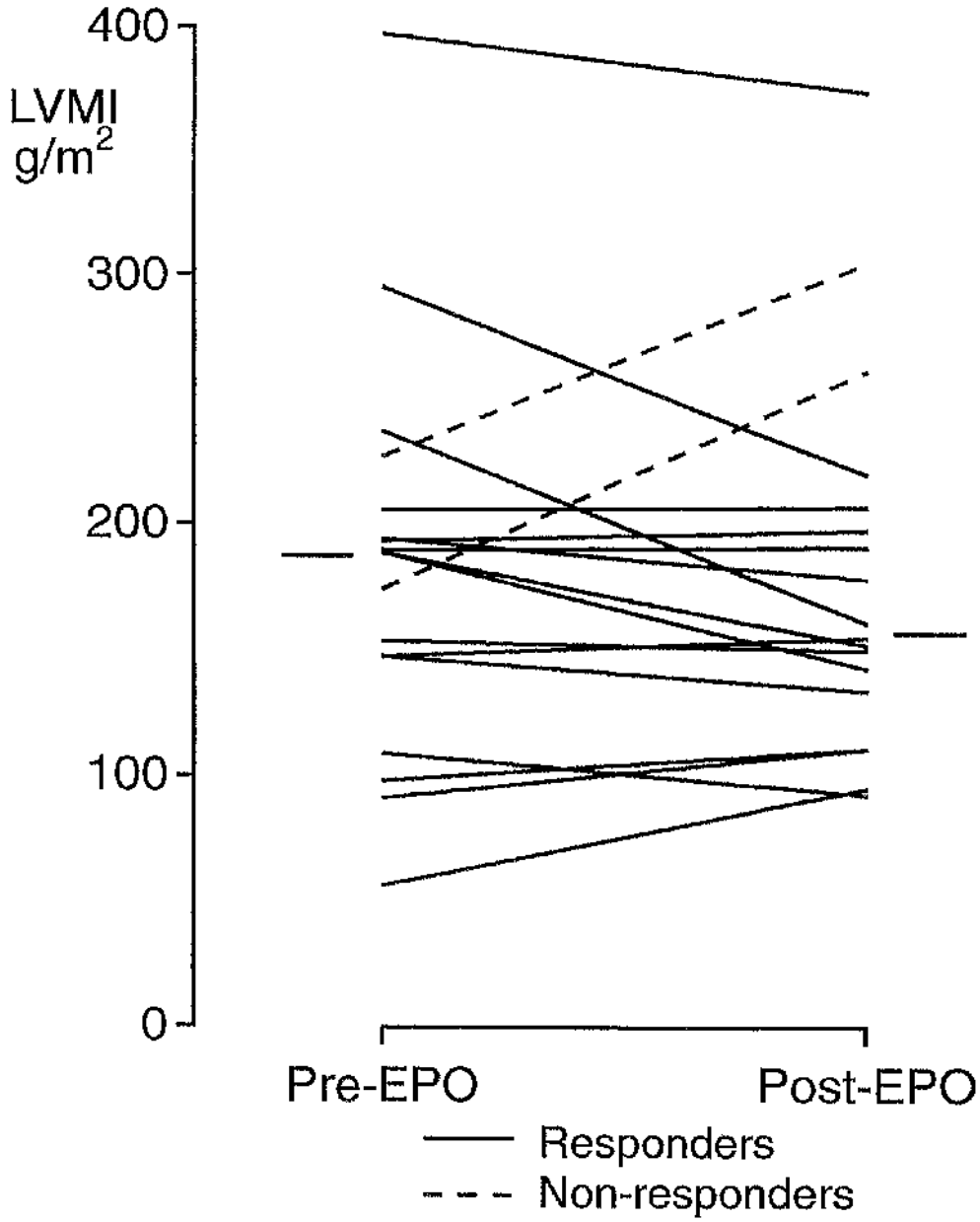

Figure 18

Change in left ventricular mass indices in patients receiving erythropoietin

	PRE-EPO	POST-EPO	95% CI p
BSAmean±SD	1.67±0.25	1.68	ns
SBP median	143	145	ns
DBP median	83	85	ns
BPdrugsmean±SD	0.87±1.0	1.4±1.2	(0.07-0.995) p=0.027
Hb median	6.8	10.3	(2.1-3.95) p=0.001
PTH pmols/l	11.5	16	ns
CA x PO4	4.9	5.0	ns

Table 33 Erythropoietin responders only (n=16)

Although a tendency for ventricular wall thickness and LV mass to fall was evident, the magnitude of change was small, possibly because of the small number of patients tested (table 34). The rise in end-systolic volume did achieve statistical significance, but the clinical significance of this is uncertain.

median	*	PRE-EPO	POST-EPO	95%CI p
IVSTcm	0	1.6	1.5	ns
PWTcm	0	1.0	0.9	ns
EDDcm	0	5.4	5.3	ns
ESDcm	0	3.4	3.8	ns
LVMIg/m^2	0	188	152	ns
EDVml	5	169	182	ns
ESVml	5	79	86	(-97- -52)p=0.006
E:A ratio	2	1.1	1.04	ns

Table 34 LV dimensions of patients who responded to erythropoietin

Section 3 Blood viscosity and erythropoietin

Blood viscosity measurements were made in 10 of the erythropoietin treated patients, all of them responders (table 35). The whole blood viscosity increased slightly, but not significantly and the plasma viscosity remained unchanged. In all other respects this group of 10 patients was similar to the complete erythropoietin group. There was found to be a negative correlation between change in blood viscosity and change in LV mass (r=-0.507).

median	*	PRE-EPO	POST-EPO	95% CI p
SBP	-	140	140	ns
DBP	-	81	85	ns
BP drugsmean	-	1	1.2±1.5	ns
Hb	-	6.6±0.6	10.4±1.2	(2.50-4.30) p=0.006
Whole BV	-	2.02	2.25	ns
Plasma V	1	1.31	1.30	ns
IVSTcm	0	1.5	1.4	ns
PWTcm	0	0.9	0.9	ns
EDDcm	0	5.4	5.4	ns
LVMIg/m^2	0	150	141	ns

Table 35 Blood viscosity (BV) (mPA.s) changes with erythropoietin

Section 4 Discussion

The patients described in this chapter were amongst the first to benefit from treatment with recombinant human erythropoietin. Of the eighteen patients who were able to continue therapy, sixteen responded, all with an improved sense of well-being and a significant rise in haemoglobin. Despite a need for more anti-hypertensive medication, and by implication, higher blood pressure, there was a trend for LV mass in these patients to fall.

In contrast LV mass increased in the two patients who did not respond to erythropoietin with a rise in haemoglobin. Although the

numbers are small, the observations suggest that successful erythropoietin therapy leads to a change in the determined LV mass, which could be interpreted as regression of ventricular hypertrophy. However, a paradoxical, albeit small increase was seen in wall thickness. Despite these changes in LV dimensions which might be expected to influence diastolic ventricular function, the E;A ratios did not alter.

Diastolic dimensions (end-diastolic diameter and end-diastolic volume) of the ventricle before and after erythropoietin were similar, but a significant increase in end-systolic volume was observed with treatment. This too is surprising because if anaemia is genuinely associated with an increase in cardiac output, then its correction might be expected to result in lower end-diastolic and end-systolic volumes. A possible explanation is that the hypoxic vasodilatation of the anaemic state is abolished with erythropoietin therapy, increased peripheral vascular resistance results and as a consequence of this and the elevated blood pressure, the heart dilates. Loss of the heightened contractility associated with anaemia might also contribute (253, 254).

The end-diastolic volume and end-systolic volume in the survey of anaemic dialysis patients, tended to be lower in patients with higher haemoglobins. However few of these patients were receiving erythropoietin. Perhaps the combined effects of erythropoietin treatment, with its pressor action, and the resolution of anaemia are important in explaining these contradictory findings.

Silberberg in his study of anemic dialysis patients, commented only upon increased ventricular mass with more severe degrees of anaemia, and did not quote measurements of diastolic or systolic cardiac size (208).

Since this Glaswegian study was performed, other investigators have reported regression of ventricular hypertrophy with erythropoietin

therapy in small groups of patients (345, 346, 347, 348), using the same LV mass formula. While Canella's patients' reduction in LVMI was accompanied by variable changes in wall thickness and end-diastolic dimension (346, 347), Zehnder's patients showed a significant reduction in interventricular septal thickness (348). The changes were confined to only the patients whose blood pressure was well controlled. Posterior wall thickness did not change and he did not quote figures for end-diastolic dimension. It is not clear whether the echo analysis was performed blindly.

On the basis of this type of work, it is now widely accepted that erythropoietin therapy leads to regression of left ventricular hypertrophy. Whether this is a valid conclusion in the presence of changing wall and cavity size, remains to be discussed.

The haemoglobin response to recombinant erythropoietin is less than that seen with naturally occuring erythropoietin from a renal transplant. This might result from cautious dosing to avoid side-effects and costs, but immunosuppression in transplant patients could theoretically modify the production or action of erythropoietin though cytokine mediated effects in transplanted patients. Such a mechanism might explain the polycythaemia which is seen in 10 to 15% of transplant recipients. As well as a greater increase in haemoglobin, whole blood viscosity also rose further, but no more than would be expected with a rising haematocrit.

The ventricular effects of a rising haemoglobin in erythropoietin treated patients and transplanted patients are less clearly matched. There was a weak relationship between change in haemoglobin and change in LV mass in the transplanted patients with a correlation coefficient of 0.318. Despite the more uniform trends in ventricular change in the erythropoietin treated patients, there was no correlation (r=-0.008). A

negative correlation between change in blood viscosity and change in LV mass index was found, which conflicts with Devereux's views on the association of blood viscosity and LV mass in hypertensive patients without renal failure (107).

Chapter 9

HYPERPARATHYROIDISM AND THE LEFT VENTRICLE

As hyperparathyroidism may predispose towards left ventricular hypertrophy and dilatation (274), and parathroidectomy in primary hyperparathyroidism is known to lead to a small reduction in LV mass (129), the effect of parathyroidectomy in uncontrolled hyperparathyroidism associated with chronic renal failure was investigated.

Twelve patients were studied before and after parathyroidectomy. Five were on dialysis and six had functioning renal transplants. One patient who had parathyroidectomy performed as a dialysis patient received a cadaveric renal transplant a month later and was included in the transplant group. The main indication for parathyroidectomy was refractory hypercalcaemia associated with inapproprately high circulating PTH levels. In dialysis patients such hypercalcaemia usually precludes use of calcium containing phosphate binders and renders control impossible without resorting to aluminium containing potentially toxic compounds. Use of vitamin D preparations is also limited by hypercalcaemia.

The mean interval between the first and second echo was 21 (±3.8) weeks.

The routine surgical procedure at the time of the echo studies was subtotal parathyroidectomy with subcutaneous implantation of a fragment of parathyroid tissue in the leg. Surgery resulted in a significant fall in PTH levels (table 36) without any significant change in blood pressure or haemoglobin.

	PRE-PTX	POST-PTX	
BSA mean±SD	1.76±0.18	1.74±0.19	ns
SBP median	135	137	ns
DBP median	82	77	ns
BP drugs mean±SD	1.0±0.74	0.92±0.1	ns
Hb median	10.3	10.0	ns
PTH pmols/l	96	4	(-134--48) p=0.003
CA x PO4	3.7	3.4	ns

Table 36 Patient characteristics before and after parathyroidectomy

median		PRE-PTX	POST-PTX	95%CI p
IVSTcm	1	1.5	1.3	ns
PWTcm	1	1.0	0.9	ns
EDDcm	1	5.1	5.4	ns
ESDcm	1	3.7	3.8	ns
LVMIg/m^2	1	150	141	(-27.9--2.1) p=0.029
EDVml	2	125	121	ns
ESVml	2	49	47	ns
E:A ratio	1	1.1	1.2	ns

Table 37 LV dimension and parathyroidectomy - all patients

Both the interventricular septal wall and the posterior ventricular wall decreased slightly, though not significantly in size (table 37). The

derived LVMI however did show a significant reduction (figure 19). No volume changes were apparent.

In case ventricular changes after parathyroidectomy are influenced by transplant status, the transplant and dialysis groups were examined separately.

Section 1 Parathyroidectomy in dialysis patients

In the dialysis group, phosphate control in the pre-operative situation was difficult, typified by the high median calcium-phosphate product. With removal of parathyroid tissue, PTH levels fell and phosphate control improved (table 38). Trends for septal thickness and LV mass to diminish were still evident (table 39).

	PRE-PTX	POST-PTX	
BSA mean±SD	1.69±0.17	1.74±0.17	ns
SBP median	133	133	ns
DBP median	77	71	ns
BP drugs mean±SD	0.6±0.54	0.2±0.4	ns
Hb median	9.1	9.0	ns
PTH pmols/l	39	7.	(-261--110) p=0.059
CA x PO4	6.1	3.8	ns

Table 38 Characteristics of 5 dialysis patients undergoing parathyroidectomy

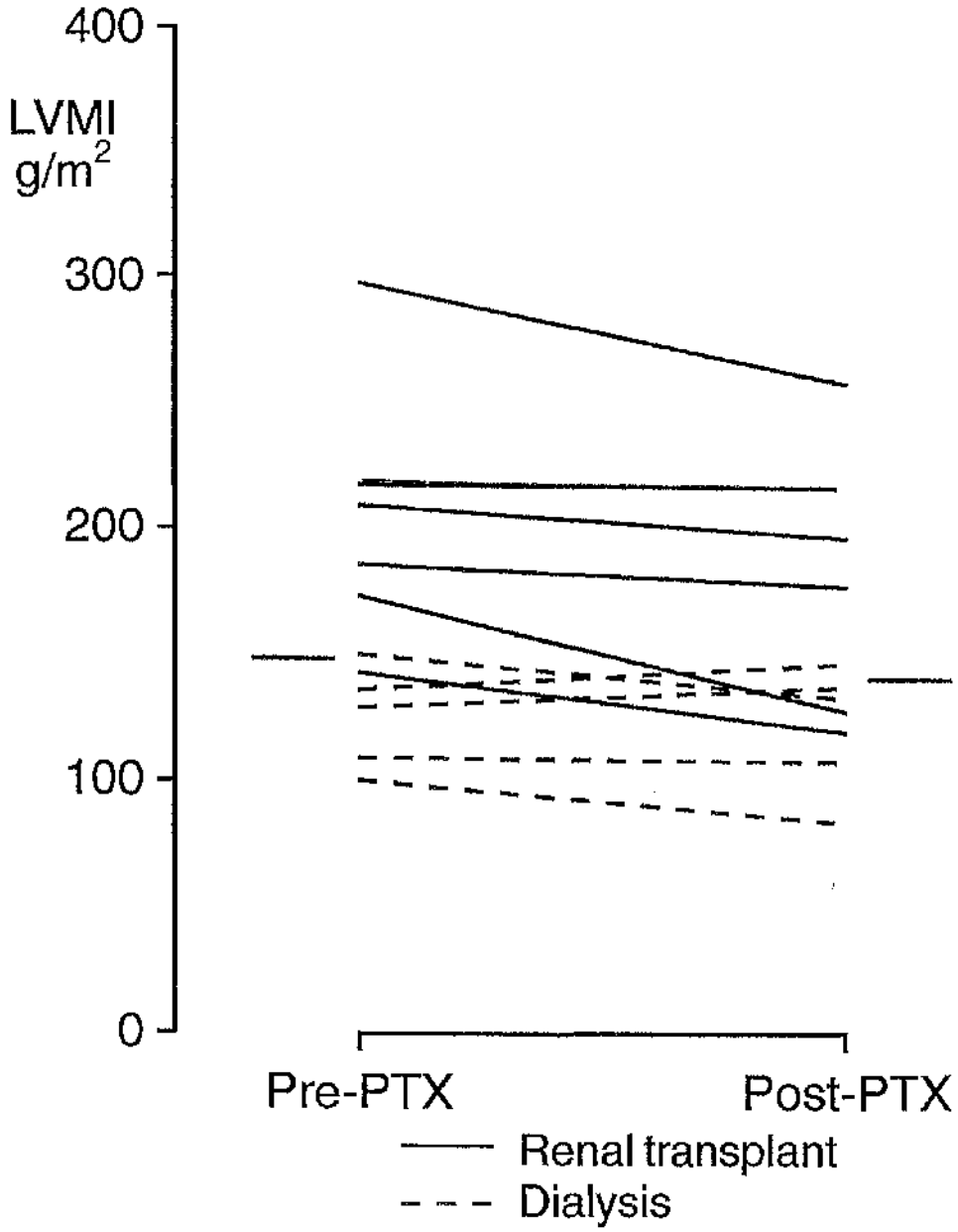

Figure 19

Changes in left ventricular mass indices in patients before and after parathyroidectomy

median	*	PRE-PTX	POST-PTX	95%CI p
IVSTcm	0	1.5	1.3	ns
PWTcm	0	1.1	1.1	ns
EDDcm	0	5.1	5.6	ns
ESDcm	0	3.3	3.6	ns
LVMIg/m^2	0	185	176	(-45.9--9.4) p=0.059
EDVml	0	132	124	ns
ESVml	0	62	45	ns
E:A ratio	1	1.4	1.1	insufficient data

Table 39 LV dimensions of 5 dialysis patients before and after parathyroidectomy

Section 2 Parathyroidectomy in renal transplant patients

In the transplanted patients, parathroidectomy did not result in any change in LV size or mass (table 41). Unlike the dialysis group there was a slight increase in the number of blood pressure lowering drugs required.

	PRE-PTX	POST-PTX	
BSAmean±SD	1.81±0.19	1.84±0.21	ns
SBP median	135	143	ns
DBP median	83	85	ns
BP drugs mean±SD	1.28±0.76	1.42±0.97	ns
Hb median	10.9	11.6	ns
PTH pmols/l	24	2	(-104--9.0) p=0.022
CA x PO4	2.8	2.3	ns

Table 40 Characteristics of 7 transplant patients undergoing parathyroidectomy

median		PRE-PTX	POST-PTX	95%CI p
IVSTcm	0	1.5	1.3	ns
PWTcm	0	0.9	0.8	ns
EDDcm	0	5.1	5.3	ns
ESDcm	0	3.8	3.9	ns
LVMIg/m^2	0	125	120	ns
EDVml	1	125	120	insufficient data
ESVml	1	48	48	insufficient data
E:A ratio	3	0.97	1.2	insufficient data

Table 41 LV dimensions of transplant patients before and after parathyroidectomy

Section 3 Discussion

Parathyroidectomy in this group of patients was associated with a reduction in the derived left ventricular mass. However, this observation did not apply in smaller subsets Nevertheless, there was a strong correlation between the change in LVMI and the change in parathyroid hormone concentration ($r=0.843$ for whole group, $r=0.5$ for dialysis patients and $r=0.97$ for transplant patients). Effective removal of parathyroid tissue will inevitably result in a fall in PTH, but the strong correlation with change in LVMI was surprising because of the variabilty of this determinant in the other studies.

Although there was a tendency for the end-diastolic dimension to increase after surgery, it is difficult to draw firm conclusions on the basis of the small number of patients. There was also a suggestion that the dialysis patients whose median LVMI tended to fall needed fewer anti-hypertensive drugs after parathyroidectomy, while the transplant patients, whose LVMI did not change needed more.

In other smaller studies of the left ventricle after parathyroidectomy in patients on renal replacement therapy, dialysis patients have been studied (277, 278, 276) with conflicting results. Neither Gafter in a series of cardiac assessments over 6 months, nor Zucchelli at 5-8months post-parathroidectomy found any significant changes (277, 278). On the other hand Druecke reported a significant early improvement in systolic function within a fortnight of surgery (276). He performed echocardiography but did not describe LV mass. Reduction in LV mass following parathyroidectomy in patients on RRT has hitherto not been described.

Chapter 10

DISCUSSION AND FINAL CONCLUSIONS

The first evidence of the importance of left ventricular hypertrophy as a risk factor for death from cardiovascular disease and other causes in patients with end-stage renal disease was presented when this thesis project was just beginning (48). At that time several small uncontrolled studies suggested renal transplantation resulted in a significant reduction in left ventricular mass (321, 322, 295, 323, 324) but the mechanism was not understood. Dialysis patients were known to have multiple problems such as hypertension, anaemia and volume overload which might predipose to cardiac failure, but the relative importance of these, particularly in relation to cardiac hypertrophy in renal disease, was unclear.

If left ventricular hypertrophy improved following renal transplantation, a study of some of the associated changes in patients not undergoing transplantation might provide insight into the mechanisms. The introduction of recombinant human erythropoietin provided the opportunity to look at correction of anaemia not attributable to improvement in renal function. The study of patients undergoing parathroidectomy made it possible to compare the cardiac effects of correcting hyperparathyroidism with those in transplanted patients. Consecutive patients undergoing renal transplantation were studied whenever possible and dialysis patients, who were subjected to none of these interventions were intended to form another control group.

At the start of the study, Devereux and Reichek's (51) method of determining left ventricular mass was regarded as the best, because it

had been validated and there was considerable experience of its utility. Ventricular diastolic dysfunction was examined in these patients, by means of Doppler transmitral flow, because of the lack of evidence of its prevalence in renal dialysis patients, the majority of whom have left ventricular hypertrophy. End-diastolic and end-systolic volumes were also assessed by a simple echocardiographic technique which has not been applied in dialysis populations before. The author performed all echo-doppler examinations herself and towards the end of the study analysed tracings which had been coded anonymously. Echocardiographic and analytical techniques were shown to be reproducible.

During the study, a randomised controlled trial of the prostaglandin analogue misoprostol was commenced and trial subjects were included in the echocardiographic survey.

As most of the patients for whom transplantation, erythropoietin therapy or parathyroidectomy was planned, were established on dialysis treatment, a cross-sectional analysis of this dialysis population was undertaken. Key investigations in the renal field have been performed in this manner (208, 349) and the comparative data provided useful background information as well as pointing to the types of effects dialysis might have on LV morphology, which would merit further study.

Section 1 Dialysis

Men were found to have greater left ventricular masses than women, despite adjustment for body surface area. This has been suggested in studies of normal subjects (91) but in male dialysis patients the differences appear greater, thus highlighting the importance of examining male:female ratios in echocardiographic surveys of dialysis patients. Echocardiographic examination is recommended, because the

two electrocardiographic methods of diagnosing left ventricular hypertrophy proved in this study to have unacceptably low sensitivities and specificities in this dialysis population.

A tendency for LV mass to increase with age was confirmed, and the influence of underlying disease on LV mass, particularly with reference to the prevalence and severity of hypertension, was illustrated. In contrast to other evidence (203), no differences between LV size in haemodialysis and CAPD patients were identified. A suggestion that LV wall thickness might increase with duration of renal replacement therapy was not confirmed by serial echocardiography in stable dialysis patients. However longer term follow-up might alter this conclusion (295, 202). Nevertheless, considerable variablity in LV mass was observed that was difficult to explain, but appeared to correlate with changes in systolic blood pressure and to a lesser extent haemoglobin. In the dialysis group, increasing severity of anaemia, tended to be associated with a thicker inter ventricular septum and a greater LV mass. End-diastolic and end-systolic volumes were larger in the most anaemic patients with haemoglobins of less than 6g/dl.

Section 2 Renal transplantation

The changes in left ventricular mass which resulted from renal transplanation were intended to form the central focus of this thesis. However, "blinded" echo analysis did not reveal the expected early reduction in LV mass. Instead LV mass changed in a fashion that could not be explained by the duration of the follow-up interval or the level of renal function achieved by the transplant. The prostaglandin analogue misoprostol did not appear to influence the change in LV mass, but may have been associated with a greater reduction in end-diastolic volume.

There was also a suggestion that patients with functioning vascular access after renal transplantation, had persisting elevation of both end-diastolic and end-systolic dimensions. The degree of change in end-diastolic dimension differed between patients who were very anaemic at the time of transplant surgery and those who were not. As the end-diastolic dimension is a component of the cube formula used to determine left ventricular mass, these observations are likely to be relevant.

Diastolic dysfunction was common and did not improve after renal transplantation, as judged by E:A ratios. Systolic function was not assessed because of the well known difficulties in interpreting the influence of preload upon observed changes (300). However, tests of diastolic function such as transmitral flow may be equally subject to variation in left ventricular end-diastolic pressure and systolic load and function (165, 166). The role of this method in the study of dialysis patients requires further evaluation before reduced E:A ratios are regarded as significant.

In a multiple logistic regression analysis of factors which might be associated with left ventricular mass at the time of renal transplantation, systolic blood pressure and male sex were found to be significant. Haemoglobin was of borderline significance, but a negative correlation between change in haemoglobin and change in LV mass after transplantation suggested a definite association.

The only variable which was found to be associated with patient outcome in this series was age at the start of dialysis treatment. Left ventricular mass index per se was not a risk factor, which contradicts Silberbergs view (48). Fundamental differences in study design might explain these discrepancies - he looked at relative risk based on quintiles of left ventricular mass index, rather than at mass as a continuous

variable, and he assessed a cohort of patients beginning renal replacement therapy, rather than a group selected for transplantation.

Section 3 Erythropoietin

In patients who responded to erythropoietin treatment, slight reductions in LV wall thickness, end-diastolic dimension and LV mass were seen. A contrasting increase in LVMI was evident in the two non-responders, but despite these changes the correlation between change in haemoglobin and change in LV mass index was not strong. This suggests other factors had a role. A rise in blood pressure with erythropoietin therapy (as judged by a need for more antihypertensive medication) or the increase in whole blood viscosity were considered as possible opposing forces to ventricular regression. However the change in whole blood viscosity exhibited a negative correlation with LV mass and the blood pressure measurements were too imprecise to be conclusive. A further study including more patients and viscosity measurements with 24 hour blood pressure recordings would be of interest.

In other reports of regression of LV hypertrophy with erythropoietin (345, 350,346, 347, 348) there have been inconsistent changes in wall thickness and cavity dimension. The relative contribution of each to the overall mass reduction should be further examined before a final judgement on erythropoietin's effect on hypertrophy can be given.

Section 4 Parathyroidectomy

Parathyroidectomy resulted in a significant fall in overall left ventricular mass, more pronounced in dialysis patients. While some slight reduction in LV mass has been demonstrated after surgical

parathyroidectomy for primary hyperparathyroidism (129), this has not been reported in patients on renal repacement therapy. London et al have reported an "inadequate left ventricular hypertrophy" in patients with severe secondary hyperparathyroidism (274) who have a degree of left ventricular dilatation and hypertrophy, but a reduced mass to volume ratio compared to dialysis patients without hyperparathyroidism. The interpretation of volume to mass ratios with the current methodology requires careful scrutiny.

In order to explain the differences in this series of studies and others in the literature, the validity of the Devereux and Reichek's (51) formula for determination of LV mass in dialysis patients was questioned. Would volume changes alone during a dialysis session influence the result?

Section 5 Volume removal and LV measurements

Echocardiographic examination was performed before and after a haemodialysis session which involved weight reduction by ultrafiltration in twenty patients. The analysis was performed blindly (table 42).

median	PRE-DIAL	POST-DIAL	95%CI p
SBP	142	128	(-37 - -60) p=0.011
DBP	78	68	(-18 - -40) p= 0.012
WEIGHT	61.9	58.5	(-3.15 - -2.0) p<0.001
XS wt	2.2		
H Rate	71	85	(3.0-11.5) p=0.015
IVSTcm	1.6	2.0	(0.13-0.555) p=0.003
PWTcm	1.0	1.1	(0.03-0.235) p=0.04
EDDcm	5.3	4.9	(-0.765- -0.05)p=0.031
ESDcm	4.1	3.5	(-0.665- -0.065) ns
LVMg	276	334	(2.5-78) p=0.042
EDVml	157	155	ns
ESVml	78	58	(-28.0 - -7.1) p=0.018
E:A	1.02	1.03	ns

Table 42 Pre- and post- dialysis data in 20 patients

Haemodialysis with weight loss was sufficient to alter the left ventricular mass significantly as assessed by Devereux's method. It changed by more than 10% in 14 of the 20 patients and was most closely associated with a change in the interventricular septal thickness (correlation coefficient r=0.742). However, significant changes in posterior wall thickness and end-diastolic and end-systolic diameters were also seen. Although the median LV mass rose, mass increased in twelve patients and decreased in eight. There was also variability in interventricular septal wall thickness.

These findings indicate that simple measurements of wall thickness and application of a cube formula to determine left ventricular mass in

dialysis patients are unreliable because volume changes alone will affect the results. This was demonstrated in the case of one of the study patients who died seventeen days after his dialysis assessment. His echocardiographic LVM was 496g before dialysis and 535g afterwards. At post-mortem the weight of the dissected left ventricle was only 380g (figure 20).

Devereux's method (51) was formulated to take account of the influence of end-diastolic diameter on the cube calculation, but in patients who are subject to volume changes, the simple subtraction technique appears inaccurate. It is presumed that a degree of ventricular wall stretching around the dilated cavity leads to apparent thinning, and removal of excess circulating volume restores ventricular wall thickness. However, this might be over simplistic as only weak correlations between changes in weight during dialysis and changes in derived left ventricular mass (r=-0.344) and interventricular septal thickness (0.021) were evident.

None of the left ventricular wall or cavity measurements remained constant, suggesting that no single measurement can be used with confidence in serial echocardiographic evaluation in dialysis patients. If relatively minor weight loss in dialysis patients can cause such profound alterations in echocardiographic indices, the effects of diuretic treatment in hypertension might also lead to false conclusions about regression of hypertrophy with treatment.

Devereux and Reicheck's original formula was and could only be validated for single, rather than serial assessments. Serial echocardiographic measurement must take into account the possible influence of changing intravascular volume.

In dialysis patients, more reliable measurements might be obtained if echocardiography were always performed at the patient's dry weight.

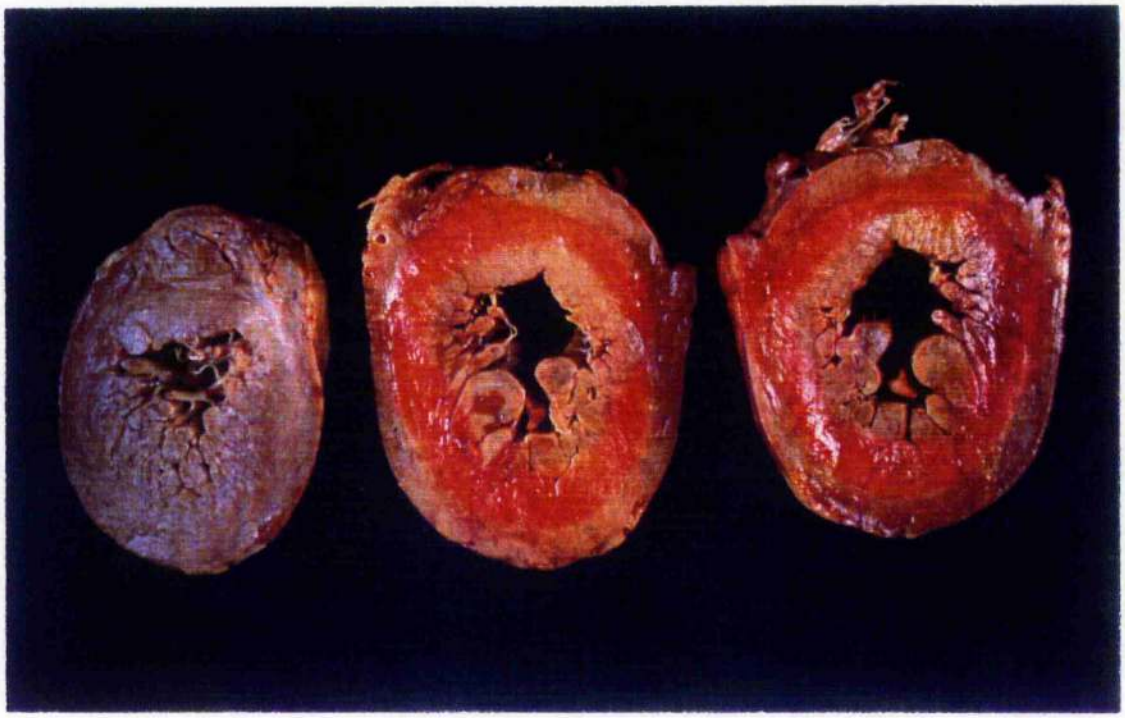

Figure 20

Sections of the left ventricle of a study patient at post-mortem. The dissected left ventricle and interventricular septum weighed 380g.

However, accurate definition can be difficult. It has been suggested that the diameter of the inferior vena cava at the point where closure is evident can be used to define euvolaemia (personal discussion with Professor Eberhardt Ritz, Heidelberg, September 1994). There may even be scope for defining ideal dry weight in terms of optimum end-diastolic diameter or interventricular wall thickness, but further study is required, initially with repeated echo measurements of LV dimensions at different body weights in the same dialysis patient.

The end-diastolic and end-systolic volumes were also affected by fluid removal during dialysis

Section 6 Final conclusions

A variety of observations were made in the course of this project which was planned and executed according to the validated and most reliable techniques available at the time. The final study of LV mass before and after haemodialysis was performed in an attempt to explain differences between the findings of this thesis and other published reports. It proved to be the most interesting aspect of the overall project, as it challenged the established methodology for determining LV mass in dialysis patients. All previous descriptions of changes in left ventricular mass must now be reviewed in the light of these results. Even the definition of cardiac hypertrophy as a risk factor should be questioned as the cube formula is now known to be an unreliable tool in patients on RRT (48).

However, the risk associated with "left ventricular hypertrophy" - be it hypertrophy or ventricular dilatation - still exists. Echocardiographic analysis continues to be useful, although its value in serial studies will be limited unless care is taken to ensure patients are in a euvolaemic state.

These conclusions may not be restricted to dialysis patients - short term studies of diuretics and vasodilator therapy on LV mass deserve further attention. Future research should aim to define individuals "dry" body weights before attempting to assess ventricular mass.

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Appendix 1 Normal biochemical and haematological ranges

	NORMAL RANGE	
sodium	135-144	mmols/l
potassium	3.5-5.1	mmols/l
bicarbonate	22-32	mmols/l
creatinine	60-110	umols/l
calcium	2.2-2.65	mmols/l
corrected calcium	2.16-2.53	mmols/l
phosphate	0.8-1.45	mmols/l
calciumxphosphate	1.76 to 3.84	
albumin	36-50	g/l
alkaline phosphatase	35-130	U/l
PTH	<6	pmols/l
haemoglobin	13-18 (male) 12-16 (female)	g/dl

Appendix 2 **Reference ranges for viscosity**
(corrected for body temperature 37°C)

	MALE mPA.s±2SD	**FEMALE** mPA.s±2SD
whole blood	3.52±0.49	3.18±0.48
plasma	1.33±0.10	1.32±0.09

Appendix 3 Normal cardiac chamber and Doppler measurements

Normal cardiac chamber sizes
(means and ULN = upper limit of normal)

	MALE	ULN	FEMALE	ULN	Ref
EDDcm	4.9	5.8	4.4	5.3	d1
ESDcm	3.1	4.1	2.7	3.7	d1
IVSTcm	1.0	1.3	0.9	1.2	d2
PWTcm	0.9	1.2	0.8	1.1	d2
LADcm	3.3	4.2	3.2	3.9	d1
LVMg	176	266	121	201	d2
LVMIg/m^2	89	134	69	109	d2

E:A ratios of diastolic LV filling in healthy adults (165)

AGE years	20-29	30-49	50-74
E:A±SE	2.7±0.4	2.0±0.3	1.2±0.2

Appendix 4 Patient details
overleaf

NAME	SEX	BIRTH	ECHOES		DISEASE	MI	HT	RRT			DURATION		OUTCOME		
				Number Type		Renal	Heart				Pres	Past	Tx	(months)	Death
A M	F	15.1.69	1	D1,T1	84				H			1	21		24.1.89	
A M	F	16.4.29	3	D2		20				H				5		A
A C	M	3.1.61	2	D1,T2	10				H				24		A	
A P	M	22.6.57	2	D1,T2	10				H				14		A	
A G	M	11.2.29	1	D1,T1	41	1		1	P			2	93		23.7.90	
A G	M	10.7.64	2	D1,E2	20			1	P				8		A	
A M	M	29.3.34	1	D1,T1	10	1		1	P				52		28.10.92	
A C	M	15.2.36	1	D1,T1	20				H				36		A	
A G	M	1.2.46	3	D1,T3	84	1		1	H				18		A	
A N	M	21.1.32	2	D1,T2	41	1	1	1	H			1	57		A	
A G	F	28.9.45	2	P2		20			1	P			1	25		A
A F	F	11.5.44	3	D2,P2	71			2	H	P			162		A	
A M	F	1.6.23	1	D1,T1	41			1	H	P		1	89		8.1.91	
A M	F	31.7.54	1	D1,T1	0			1	H				7		A	
A B	M	17.8.39	2	D2		80			1	H	P		1	52		A
A B	M	20.4.66	1	D1,T1	86				H	P			30		A	
A M	M	6.10.51	1	D1,T1	10			1	H	P		1	70		A	
A W	M	10.10.70	1	D1,T1	20				H			1	51		A	
A J	F	10.5.63	2	D1,T2	83			1	P				16		A	
A M	F	27.5.56	3	D1,T3	50			1	H			1	69		A	
A M	M	9.9.64	1	D1,T1	10				H	P		1	33		A	
A H	M	26.7.41	2	D1,T2	73			1	P				14		A	

NAME	SEX	BIRTH	ECHOES		DISEASE	MI	HT	RRT			DURATION		OUTCOME		
				Number Type		Renal	Heart			Pres	Past	Tx	(months)	Death	
B P	F	23.12.59	2	D1,T2^{+}	20				H			4		A	
B M	M	14.4.59	3	D2,T2	20			1	H		3	121		A	
B E	M	7.4.39	1	D1,T1	10			1	H			21		A	
B S	M	25.11.58	2	D2		80		1	H				0		A
B C	F	1.7.22	1	D1		20	1	1	H				0		2.9.91
C M	M	5.5.67	2	D1,T2	10			2	P			38		A	
C M	M	26.11.62	2	D1,E2	80	1		1	P		1	8		16.7.91	
C L	M	17.11.55	1	D1		0	1		1	H			45		13.9.91
C B	F	6.11.69	1	D1,T1	10			1	H			10		A	
C B	M	30.11.65	2	D1,T2	20	1		1	H			72		A	
C R	M	23.3.51	1	D1,E1^{U}	80			1	H	P		100		27.2.92	
C S	M	22.3.70	1	D1,P1	10			1	H	P	1	78		A	
C M	F	10.1.70	3	D1,E3,P1	20			1	H	P	1	84		A	
C H	F	3.6.54	3	D1,T2,P2^{+}		20			1	H			32		A
C G	M	5.9.72	1	D1		10			1	H	P	1	61		A
C D	M	25.5.72	1	P1		63			1	P	H	1	35		A
C B	M	29.3.47	2	D2		10			1	P	H	1	55		A
D M	M	4.6.46	3	D1,T3	10			1	P		0	2		A	
D M	M	2.11.42	1	D1,T1	10			1	H		0	4		17.6.91	

NAME	SEX	BIRTH	ECHOES		DISEASE	MI	HT	RRT			DURATION		OUTCOME		
			Number	Type		Renal	Heart			Pres	Past	Tx	(months)	Death	
D C	M	25.3.50	2	D1,T2	10			1	H		1	80		A	
D H	M	30.10.38	2	D1,T2	10			1	P			28		A	
D H	M	30.11.27	3	D2,T2	10	1		1	H			128		A	
D L	M	2.8.61	1	D1,T1	20			1	H		1	78		A	
D R	M	12.5.40	1	D1,T1	20			1	P			13		A	
D C	M	30.7.57	2	D1,T2	10			1	P			13		A	
D M	M	5.6.61	1	D1,T1	10			1	P			2		A	
D A	M	22.10.69	2	D1,T2	43				H			7		A	
D E	M	19.5.46	2	D1,T2	10			1	H			24		A	
E O	M	4.2.51	2	D1,T2	20				P			29		A	
E S	M	20.1.29	1	D1		71	1		2	H	P		83		A
E C	F	4.2.22	1	D1,T1[0]	20	1		1	H		1	120		A	
E N	F	24.7.56	6	D2,E2,P2	20			1	H		1	92		A	
E P	F	23.2.68	2	D1,T2	20			1	H			4		A	
E S	F	19.12.29	2	D1,T2	41			1	H			8		A	
E S	F	8.12.37	1	D1		80			1	H			0		A
E S	F	15.6.39	1	D1,T1*	10	1		1	P			28		A	
E F	F	2.6.43	1	D1,T1	20			1	P			11		A	
E S	F	20.12.39	1	D1		10			1	H	P		32		A
E B	F	13.12.48	1	D1,T1	80			1	P		1	63		A	
E Y	F	30.11.61	1	D1,T1*	20				H		1	133		A	
E M	F	3.9.40	3	D1,T3	41	1		1	H			36		A	

NAME	SEX	BIRTH	ECHOES		DISEASE	MI	HT	RRT			DURATION		OUTCOME		
				Number Type		Renal	Heart			Pres	Past	Tx	(months)	Death	
E B	M	25.12.64	3	D1,T3	86			1	H			33		A	
E H	M	19.1.50	3	D1,T3	10			1	H			23		A	
E M	M	11.4.66	1	D1,P1–	63			1	H	P	1	131		11.3.90	
F S	F	11.12.44	3	D1,E3	0				H		1	110		A	
F P	M	7.8.30	1	D1,T1	86			1	P	H		20		A	
G T	M	6.6.67	4	D1,T2,P2	0				H			10		A	
G B	M	11.9.34	2	D1,T2	0	1		1	P			24		A	
G S	M	17.7.59	1	D1,T1	80			1	P			9		A	
G H	F	8.2.37	1	D1,T1–	93				H			72		25.6.90	
G C	M	10.12.71	1	D1[0]		99			1	H			36		A
G F	M	6.6.62	1	D1,T1	10			1	H			9		A	
G M	F	24.9.47	1	P1		0	1		2	H		1	69		A
H H	M	24.11.27	1	D1		83	1	1	1	H			59		A
H B	F	1.2.52	2	D1,T2	0			1	P	H		20		A	
H C	F	27.6.41	2	D1,T2	41	1	1	1	H			21		A	
H A	M	24.7.30	1	D1		71	1		1	H			25		A
H D	M	24.8.39	1	D1,T1–	20				H	P	1	146		6.5.90	
H J	M	19.12.31	1	D1,T1–	83			1	H			3		30.11.89	
H M	M	28.9.36	2	D2		70	1		1	H			142		15.8.90
I C	M	17.3.46	4	D2,P2	20	1		1	H		1	67		28.2.92	
I H	M	26.2.65	1	D1,T1*	74			1	P			12		A	
I M	M	17.8.60	2	D1,T2	10			1	H		1	82		A	

NAME	SEX	BIRTH	ECHOES		DISEASE		MI	HT	RRT			DURATION		OUTCOME		
			Number	Type	Renal	Heart				Pres	Past	Tx	(months)	Death		
I R	M	8.1.44	3	D2,E2	20				1	P	H	2	133		A	
I B	F	20.6.61	1	D1,T1	10				1	H			18		A	
I S	F	6.7.43	1	D1,T1*	41				1	H			11		A	
I P	F	15.3.32	2	D1,T2	93				1	P			66		A	
I A	F	7.5.44	2	D1,T2	80				1	P			17		A	
J R	M	24.11.57	2	D1,E2	20	1			1	H	P	1	103		A	
J A	M	23.12.50	2	D1,T2	10	1			2	H			23		A	
J B	M	9.3.57	2	D2		0				1		H		0		A
J B	M	7.2.46	2	D2		10				1	H		1	132		30.11.88
J P	M	22.1.54	2	D1,T2	86				1	H			44		A	
J S	M	26.11.40	1	D1,T1	41					H		1	127		A	
J T	M	19.1.38	1	D1,T1⁰	71	1			2	P			12		7.4.92	
J H	F	1.5.33	1	D1,T1–	41				1	P			27		4.6.88	
J P	F	25.8.37	2	D1,T2	20	1		1	1	H		1	133		A	
J P	M	20.7.30	3	D1,T3	20				1	H			60		A	
J B	F	15.8.38	3	D1,T2,P2	20				1	H			10		A	
J R	F	12.2.57	2	P2		20				1	H		2	92		A
J L	F	9.2.42	2	D1,T2	10					H		1	136		A	
J R	F	2.12.53	1	D1,T1	10				1	P	H		8		A	
J M	F	25.4.68	2	D1,T2	62				1	H	P	1	108		A	
J B	M	26.9.53	2	P2		20				1	H		1	86		A
J D	M	14.4.57	1	D1,T1*	0					H			8			

NAME	SEX	BIRTH	ECHOES		DISEASE		MI	HT	RRT			DURATION		OUTCOME		
			Number	Type	Renal	Heart				Pres	Past	Tx	(months)	Death		
J D	M	29.6.42	1	D1,T1	41	1			1	P			43		A	
J E	M	11.2.37	2	D1,T2	41	1			1	P			48		7.4.91	
J G	M	27.10.43	2	D1,E2	86				1	H			15		A	
J H	M	6.10.51	2	D1,T2	80	1			1	P			11		A	
J K	M	29.5.63	1	D1,T1	10				1	P			3		A	
J L	M	19.12.57	1	D1,T1	10				1	H			7		A	
J M	M	17.4.41	3	D1,T3	41				1	H			43		A	
J M	M	2.3.65	3	D2,T2	20				1	P			21		A	
J M	M	6.6.63	5	D2,E3	10				1	H	P	2	83		A	
J M	M	20.5.58	1	D1,T1	71				2	H			23		A	
J M	M	16.6.52	2	D1,T2	10				1	H			10		A	
J N	M	25.5.55	2	D2,T1–	54				1	H			11		12.11.90	
J O	M	17.11.47	1	$D1,T1^0$	51				1	H			12		A	
J R	M	23.3.55	1	D1,T1	10				1	P			5		A	
J C	M	20.4.34	1	P1		92		1			H		1	106		25.6.90
J C	M	17.1.53	1	D1,T1	51				1	H		1	149		26.7.92	
J A	F	29.4.32	2	D1,T2	41	1			1	H		2	108		A	
J R	F	30.6.30	1	D1,T1–	41				1	P			22		26.9.90	
J M	F	23.10.62	2	D1,T2	20					H			21		A	
J B	M	19.9.70	4	P2,T2		20				1	H			14		A
J B	F	21.8.56	1	$E1^0$		10				1	P		1	60		A
K C	F	9.5.38	2	D1,T2	20	1				H			48		A	

NAME	SEX	BIRTH	ECHOES		DISEASE		MI	HT	RRT			DURATION		OUTCOME		
			Number	Type	Renal	Heart				Pres	Past	Tx	(months)	Death		
K M	F	6.5.30	2	D1,T2	10	0	0	1	2		1	62		A		
K N	M	8.6.58	1	D1		51	0	0	1	2	1	1	79		A	
K W	M	22.4.64	1	D1,T1	84	0	0	1	1	0	0	9		A		
L C	F	12.10.70	2	D1,T2	0	0	0	1	2	0	0	4		A		
L A	F	11.11.24	1	D1,T1	41	1	0	1	1	0	0	65		12.12.91		
L B	F	29.1.44	1	D1,T1	0	0		0	1	0	0	21		A		
L C	F	20.3.40	1	D1,T1	80	0	0	0	2	0	0	10		13.5.89		
L S	F	1.3.58	4	D1,E3,T2	10	0	0	1	1	0	0	6		A		
M C	F	8.11.62	1	D1,T1	10	0	0	1	1	0	0	1		A		
M J	F	18.1.39	2	P2		72	1	0	2	2	0	0			A	
M W	F	23.11.65	1	D1,T1	60	0	0	2	1	0	0	48		A		
M M	F	1.4.52	1	D1,T1	80	0	0	0	2	0	0	5		2.7.88		
M S	F	5.11.59	2	D2		20	0	0	1	1	0	0	0		A	
M Q	F	16.12.37	2	D1,T2	72	0	0	2	2	0	0	37		A		
M K	M	21.12.49	1	D1,T1	10	0	0	1	1	0	0	46		A		
M B	F	24.5.55	2	E2		10	0	0	1	1	2	2	141		A	
M M	F	24.12.50	1	D1		20	0	0	0	1	0	1	183		A	
M M	F	14.8.22	1	D1		80	0			2	0	0	0		13.4.91	
M M	F	16.11.42	2	D1,T2	0	0	0	1	2	0	0	37		A		
M S	F	14.6.61	2	D1,T2	10	0	0	1	1	0	0	8		A		
M Y	F	2.10.38	2	D1,T2	20	0	0	1	1	0	0	72		5.7.89		
M C	M	19.3.21	1	D1,P1	70	0	0	1	0	0	0	0		A		

NAME	SEX	BIRTH	ECHOES		DISEASE		MI	HT	RRT			DURATION		OUTCOME
			Number	Type	Renal	Heart				Pres	Past	Tx	(months)	Death
M A	F	16.4.29	1	D1,T1	31	0	0	1	2	1	0	77		A
M B	F	26.9.29	1	D1,T1	20			0	2	0	0	61		22.6.89
M B	F	7.1.32	2	D1,T2	20	0	0	0	2	0	0	16		9.12.89
M B	F	9.9.55	2	D1,T2	10	0	0	1	1	0	0	13		A
M C	F	24.6.34	2	D1,E2	31	0	0	1	2	0	0	16		A
M F	F	23.10.26	1	D1,T1	72	0	0	1	1	2	0	41		A
M G	F	25.5.66	1	D1,T1	20	0	0	0	1	2	1	45		A
M H	F	29.5.48	2	D1,E2	10	0	0	1	2	0	0	30		A
M K	F	25.11.41	3	D1,T3	72	0	0	1	2	0	0	23		A
M M	F	17.12.47	2	D1,T2	20	0	0	1	1	2	1	91		A
M P	F	12.4.45	2	D1,T2	20	0	0	1	2	0	0	21		A
M S	F	25.8.39	1	D1,T1	41	0	0	1	2	0	1	29		A
M V	F	24.7.41	1	D1,T1	41	0	0	1	2	0	0	16		A
M B	M	20.5.48	3	D2,T2	80	0	0	1	2	0	1	26		A
M M	M	29.9.45	2	D1,T2	10	0	0	2	2	1	0	82		A
M S	M	6.1.62	3	D1,T3	10	0	0	0	1	0	0	28		A
M S	F	10.2.21	2	D1,P2	41	0	0	0	1	0	0	129		A
N S	M	7.2.71	2	D1,E2	10	0	0	1	2	1	1	76		A
N C	F	8.11.44	1	D1,P1	10	0	0	0	1	0	3	212		A
N H	F	21.11.72	2	D2,T1	10	0	0	0	2	0	0	7		A
N J	M	26.12.38	1	D1,T1	10	0	0	1	2	0	0	14		A
N M	M	9.5.32	1	D1,T1	10	0	1	1	2	0	0	10		A

NAME	SEX	BIRTH	ECHOES		DISEASE	MI	HT	RRT			DURATION		OUTCOME	
			Number	Type	Renal	Heart			Pres	Past	Tx	(months)	Death	
P D	F	3.11.55	1	D1,T1	99	0	0	0	2	0	0	12		A
P M	M	6.11.61	3	D2,T2	63	0	0	1	1	2	1	157		A
P L	M	8.7.34	1	D1,T1	10	0	0	0	2	1	0	22		11.2.92
P M	M	13.9.42	1	D1,E1	80	0	0	1	2	0	0	1		A
P M	M	3.5.45	2	D1,T2	10	1	0	1	1	0	0	18		A
P P	M	17.5.66	1	D1,T1	10	0	0	0	2	0	0	8		A
R K	M	25.12.37	3	D3,E1	10	0	0	0	1	2	3	129		A
R B	M	7.10.36	2	D1,T2	10	0	0	1	2	0	0	17		A
R C	M	18.6.53	1	D1,T1	51	0	0	1	1	0	1	28		A
R E	M	17.1.50	1	D1,T1	80	0	0	1	2	0	0	16		7.5.90
R I	M	3.5.34	2	D1,T2	71	1	1	2	2	0	0	28		25.6.90
R M	M	17.1.31	1	D1,T1	72	1	0	1	2	0	0	45		28.8.89
R L	M	23.1.52	2	D1,T2	50	0	0	0	2	0	0	6		18.3.92
R D	M	15.8.26	4	D3,E2	10	1		1	1	0	1	104		A
R F	M	16.11.57	2	D1,E2	20	0	0	1	2	0	1	69		A
R S	M	31.10.67	2	D1,T2	10	0	0	0	2	0	0	10		29.1.89
R L	M	24.6.39	1	D1,T1	20	1	0	0	2	0	0	40		11.7.91
S K	F	27.2.56	1	D1,T1	20	0	0	1	2	0	1	147		A
S M	F	24.2.67	2	D1,T2	20	0	0	1	2	1	0	26		A
S L	F	30.12.62	3	D3		20	1	0	1	1	0	1	185	A
S P	M	2.9.32	2	D1,T2	10	0	0	1	1	0	0	68		14.12.89
S M	M	1.10.68	1	D1,T1	20	0	0	1	1	0	1	33		15.10.90

NAME	SEX	BIRTH	ECHOES		DISEASE		HT	RRT			DURATION		OUTCOME		
			Number	Type	Renal	Heart			Pres	Past	Tx	(months)	Death		
S W	M	23.11.59	2	D1,T2	80	0	0	1	2	0	0	26		A	
T B	M	2.2.58	2	D1,E2	10	0	0	1	2	0	0	54		A	
T F	M	7.12.39	1	D1,		10	0	1	1	2	0	0	0		A
T F	M	5.1.29	2	D1,T2	10	1	1	1	1	0	0			6.12.91	
T R	M	24.5.31	1	D1,T1	20	1	1	1	2	0	0	38		16.1.91	
T S	M	25.3.52	2	D1,E2	20	0	0	1	1	0	0	53		A	
TC	M	25.6.50	3	D1,T3	10	0	0	0	2	0	0	24		A	
T T	M	4.3.54	2	D1,T2	84	0	0	1	2	0	0	25		A	
T S	F	31.7.71	2	D1,T2	0	0	0	0	1	0	0	.5		A	
U K	F	28.6.63	2	D1,T2	41	0	0	1	1	0	1	87		A	
W M	F	3.8.65	2	D2,T1	20	0	0	1	1	0	1	134		A	
W M	F	14.8.60	2	D1,T2	80	0	0	1	2	0	0	10		A	
W D	F	8.12.35	2	D1,T2	70	1	0	0	1	0	0	32		12.6.92	
W P	F	22.2.40	1	D1,T1	20	0	0	0	1	0		23		A	
W A	M	17.2.43	3	D3		10				1		1	172		A
W B	M	9.10.59	3	D1,T3	20	0	0	0	1	0	0	3		A	
W B	M	29.6.47	1	D1,T1	10	1	0	1	2	0	0	19		A	
W B	M	3.6.35	1	D1		10	0	0	1	1	2	0	29		A
W C	M	12.4.23	2	D1,T2	10	1	0	1	2	1	0	70		A	
W G	M	15.1.62	3	D1,E3	80	1	0	1	1	2	2	66		27.6.91	
W K	M	4.1.46	2	D1,T2	10	0	0	1	1	0	1	69		A	
W M	M	21.3.61	2	D1,T2	0	0	0	0	2	0	0	6		A	

NAME	SEX	BIRTH	ECHOES		DISEASE		MI	HT	RRT			DURATION		OUTCOME
			Number	Type	Renal	Heart				Pres	Past	Tx	(months)	Death
W M	M	29.5.40	1	D1,T2	80	1	0	1	2	0	0	11		A
Y R	F	5.2.60	2	D2,T1	84	0	0	1	2	1	1	62		A
Y M	F	27.5.68	3	D3,T1	52	0	0	0	1	2	0	77		A

KEY

1 = YES 0 = NO

ECHO TYPE:

D	DIALYSIS	MI	PREVIOUS MYOCARDIAL INFARCTION
T	TRANSPLANT	HT	PREVIOUS HYPERTENSION
E	ERYTHROPOIETIN	RRT	RENAL REPLACEMENT THERAPY
P	PARATHYROIDECTOMY		1=HAEMODIALYSIS, 2=PERITONEAL DIALYSIS

DISEASE:(FROM EDTA CODES)

0	CAUSE NOT KNOWN
10	GLOMERULONEPHRITIS
20	REFLUX NEPHROPATHY, PYELONEPHRITIS
31	ANALGESIC NEPHROPATHY
41	ADULT POLYCYSTIC KIDNEY DISEASE
43	MEDULLARY CYSTIC DISEASE
50	FAMILIAL NEPHROPATHY
51	ALPORTS
52	CYSTINOSIS
54	FABRY'S
60	RENAL HYPOPLASIA
63	RENAL DYSPLASIA
70)	
71)	RENOVASCULAR DISEASES
72)	
80	INSULIN DEPENDENT DIABETES
84	SLE
86	GOODPASTURES SYNDROME

OUTCOME

A = ALIVE