Prognostic and pathophysiological features of uraemic cardiomyopathy using cardiovascular magnetic resonance imaging

by

Dr Rajan Kantilal Patel

BSc (Hons), MBChB (Hons), MRCP (UK)

Renal Unit, Western Infirmary, Glasgow and
British Heart Foundation Glasgow Cardiovascular Research Centre,
University of Glasgow, UK

A thesis submitted for the degree of Doctor of Philosophy in the Faculty of Medicine of the University of Glasgow

October 2010

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List of abbreviations

2,3-DPG	2, 3-diphosphoglycerate
2DE	Two dimensional echocardiography
4D	Deutsche Diabetes Dialyse Studie
4S	Scandinavian Simvastatin Survival Study
A(II)RB	Angiotensin (II) receptor blocker
ABCD trial	Alternans Before Cardioverter Defibrillator trial
ABPM	24 hour ambulatory BP monitoring/measurements
ACE-I	Angiotensin coverting enzyme inhibitor
ADP	Adenosine diphosphate
AHA/ACC	American Heart Association/American College of Cardiology
(A)MI	(Acute) Myocardial Infarction
AP	Action potential
ATP	Adenosine triphosphate
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
β Blocker	Beta blocker
BFD	Biofeedback dialysis
BMI	Body mass index
BNP	Brain natriuretic peptide
BOLD CMR	Blood oxygen level- dependent CMR
BP	Blood pressure
Ca	Calcium
Ca x PO4	Calcium phophate product
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAPD	Continuous ambulatory peritoneal dialysis
CKD	Chronic kidney Disease
CMR	Cardiovascular magnetic resonance imaging
CRP	C reactive protein
CV	Cardiovascular
CVA	Cerebrovascular disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EBCT	Electron beam computed tomography
ECG	Electrocardiograph
EDV/BSA	Body surface area corrected end diastolic volume
EP	Electrophysiological
EPR	Electronic patient records
ESA	Erythropoetin receptor stimulating agent
ESRD	End stage renal disease
(e)GFR	(Estimated) Glomerular filtration rate

ESV/BSA	Body surface area corrected end systolic volume
Gd-DTPA	gadolinium- diethylenetriamine- pentaacetic acid
Hb	Haemoglobin
HbA1c	Haemoglobin A1C
HD	Haemodialysis
HDL	High density lipoprotein
HEMO	Hemodialysis study
HEP	High energy phosphate
HMG Co-A reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase
HRV	Heart rate variability
ICD	Implantable cardioverter defibrillator
IDH	Intradialytic hypotension
IHD	Ischaemic heart disease
IL	Interleukin
IQR	Interquartile range
IVRT	Isovolumetric relaxation time
K/DOQI	Kidney Disease Outcome Quality Initiative
K+	Potassium
KDIGO	Kidney Disease: Improving Global Outcomes
LAV	Left atrial volume
LAV/BSA	Body surface area corrected left atrial volume
LDL	Low density lipoprotein
LGE	Late gadolinium- diethylenetriamine- pentaacetic acid enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
LVOT	Left ventricular outflow tract
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II
MASTER I	Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients
MRI	Magnetic resonance imaging
MTWA	Micovolt T wave alternans
NHANES	National Health and Nutrition Examination Survey
NMV	Net magnetisation vector
NSF	Nephrogenic systemic fibrosis
NYHA	New York Heart Association
PCI	Percutaneous intervention
PCr:ATP	Phosphocreatine to beta ATP ratio
(^{31}P)MRS	(^{31} Phospohorus) magnetic resonance spectroscopy
PD	Peritoneal dialysis
Pi	Inorganic phosphate
PO4	Phosphate
Pre-D	Predialysis

PTH	Parathyroid hormone
PVD	Peripheral vascular disease
RA	Repolarisation alternans
RF	Radiofrequency
ROS	Reactive oxygen species
RRT	Renal replacement therapy
RT	Renal transplantation
RWMA	Regional wall motion abnormality
SA	Short axis
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
TGF-β	Transforming growth factor beta
TNFα	Tumour necrosis factor alpha
UF	Ultrafiltration
URR	Urea reduction ratio
USRDS	United States renal data system
VC	Vascular calcification
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VTA	Ventricular tachyarrhythmia

Acknowledgements

I would like to thank my principal supervisor Professor Alan Jardine for the opportunity to undertake this research and his excellent guidance, support and patience during these studies. I would also like to thank my co-supervisor, Professor Stuart Cobbe, for his advice, particularly with the use of cardiac electrophysiological apparatus. I am also grateful to the other members of the Renal Research Group for their support, in particular Dr Paddy Mark, for his advice and tuition throughout this project.

I am extremely grateful to Ms Tracey Steedman, Dr Gillian McNaught and Professor Henry Dargie for teaching me cardiovascular magnetic resonance imaging and spectroscopy acquisition and analyses. I would also like to thank Mr Tony Cunningham for his help obtaining echocardiography images for analyses.

I would also like to thank the Consultants of the Renal Unit for their encouragement and help recruiting patients: Miss Laura Buist, Mr Marc Clancy, Dr Conal Daly, Dr Colin Geddes, Dr Brian Junor, Mr David Kingsmore, Dr Ellon McGregor, Dr Margaret McMillan, Mr Enric Murio, Dr Neal Padmanabhan and Dr Stuart Rodger. Furthermore I would like to thank the British Heart Foundation who supported this work through a clinical research training fellowship. I am grateful to my family for their support and advice throughout my studies. I would like to give particular thanks to my father for his support and advice in the preparation of this thesis.

Finally, I am indebted to the patients of the Greater Glasgow and Clyde Renal Units who, by their willingness to participate, made this research possible.

Author's declaration

The work presented in this thesis was that of the author and his supervisors, Professor Alan Jardine and Professor Stuart Cobbe. All experimental work was carried out by the author except acquisition of echocardiographic scans (performed by Tony Cunningham, Clinical Research Initiative, University of Glasgow), and acquisition of a proportion of cardiac magnetic resonance images (performed by Tracey Steedman, Glasgow Cardiac Magnetic Resonance Unit, University of Glasgow).

I declare that this thesis has been composed by myself and is a record of work performed by myself. It has not been previously submitted for a higher degree.

Rajan Kantilal Patel

October 2010

Summary

Premature cardiovascular (CV) death is the commonest cause of death in patients with end stage renal disease (ESRD), which includes those receiving or close to requiring renal replacement therapy. In ESRD patients, CV deaths are most commonly caused by cardiac arrhythmia and sudden cardiac death compared to the general population where myocardial ischaemia and infarction predominate. Higher CV disease burden is due to accumulation of "conventional" risk factors (e.g. hypertension, diabetes mellitus, smoking) and "novel" risk factors (e.g. oxidative stress, proteinuria, anaemia, inflammation) in ESRD patients. In addition, risk factors specific to patients with renal disease have been identified including alteration in left ventricular (LV) structure, called uraemic cardiomyopathy. These structural abnormalities are common in patients with ESRD (between 60-80% of subjects upon initiation of dialysis) and include left ventricular hypertrophy (LVH), systolic dysfunction (LVSD) and dilatation. These changes in LV structure confer adverse CV outcome in ESRD patients and have proven difficult to reverse.

Detection of these abnormalities is usually performed using echocardiography, however this technique is inaccurate in ESRD patients due to significant alterations in LV shape and geometric assumptions made during calculation of myocardial mass. Cardiovascular MRI (CMR) negates these assumptions and is the most accurate, reproducible and reliable method of assessing LV dimensions independent of intravascular volume, particularly in patients with altered myocardial architecture. Furthermore, maximal left atrial volume can be measured using CMR. The principle aims of the studies presented in this thesis were to elucidate prognostic and pathophysiological features of uraemic cardiomyopathy using CMR.

In a large study (n=246) of haemodialysis patients, the determinants of each LV abnormality of uraemic cardiomyopathy were identified from past clinical history, haemodialysis and blood parameters and other LV measurements. For LV changes, major determinants were clinical features associated with advanced renal disease, namely expansion of intravascular/ extracellular fluid compartment, abnormal bone mineral biochemistry and hypertension. Furthermore, presence of one LV abnormality was one of the strongest predictors of presence of another, perhaps indicating differing stages of uraemic cardiomyopathy development. In a subsequent prognostic study including these patients (n=446), presence of LVSD and LV dilatation on CMR were significantly associated with poorer all cause and CV mortality. Presence of LVH, which is by far the most common structural change, was associated with poorer cardiovascular survival only. In addition, presence of two or three abnormalities (commonly LVH with another abnormality) had a significantly poorer prognosis and independently predicted CV and all cause mortality. This has implications for therapeutic strategies which should aim to slow or reverse cardiac changes of ESRD and prevent progression from one cardiac abnormality to 2 or more. In a further study (n=201) investigating additional prognostic features of ESRD patients with LVH, maximal left atrial volume (LAV) was measured using the bi-plane area length method at end LV systole. Elevated LAV and presence of LVSD were significantly associated with poorer all cause survival and were independent predictors of death. The most likely causes of elevated LAV in ESRD patients are LV diastolic dysfunction and expanded extracellular compartment and may provide a target for therapeutic intervention.

The electrophysiological features of uraemic cardiomyopathy were assessed using microvolt T wave alternans (MTWA) which is a novel, non-invasive method of measuring small variations in surface electrocardiogram (ECG) T wave morphology and thus ventricular repolarisation. This technique has been used to stratify other cohorts at elevated risk of sudden cardiac death (such as ischaemic and non ischaemic cardiomyopathy, hypertensive LVH). A study presented in this thesis, compared MTWA results between ESRD (n=200) and hypertensive patients with LVH on echocardiography (n=30). Abnormal MTWA result was significantly more common in ESRD patients compared to hypertensive patients with LVH. Furthermore, abnormal MTWA result was significantly associated with myocardial abnormalities of uraemic cardiomyopathy and a history of macrovascular atheromatous disease in ESRD patients. Despite preservation of LV function on CMR, the frequency of abnormal MTWA result in ESRD patients was similar to previous studies in subjects with heart failure. ^{31}Phosphorus magnetic resonance spectroscopy is a novel, non-invasive technique of estimating cardiac energetic status and high energy phosphate (HEP) metabolism in a myocardial area of interest and has previously been used to assess patients with global myocardial disease (dilated cardiomyopathy, hypertensive LVH). High energy phosphate metabolism was compared between patients with ESRD (n=53) and hypertensive LVH (n=30) and despite similar LV mass between both groups, PCr: ATP (an indicator of HEP metabolism) was significantly reduced in ESRD patients. These findings are most likely due to cardiac interstitial fibrosis and the alteration of tissue composition within the area of interest, and changes in metabolic function within cardiomyocytes of uraemic hearts. Finally, a small study (n=50) investigated the effect of successful renal transplantation on LV mass measured by CMR. On comparison of patients

who remained on the renal transplant waiting list, there was no significant difference in LV mass in patients who received a renal transplant. It is likely that previous echocardiography studies that demonstrated significant regression of LVH, measured improvement in fluid control rather that actual reduction in myocardial mass.

Future studies investigating benefit of therapeutic intervention may require identification of individuals at higher CV risk and the results of studies presented in this thesis aim to provide information for selecting such ESRD patients. With these results in mind, further prospective studies will be able to carefully select groups of ESRD patients with differing left ventricular, left atrial, electrophysiological and biochemical properties to demonstrate survival benefit with interventional agents. In this way, future therapies for ESRD patients can be tailored to improve cardiovascular survival.

Chapter 1

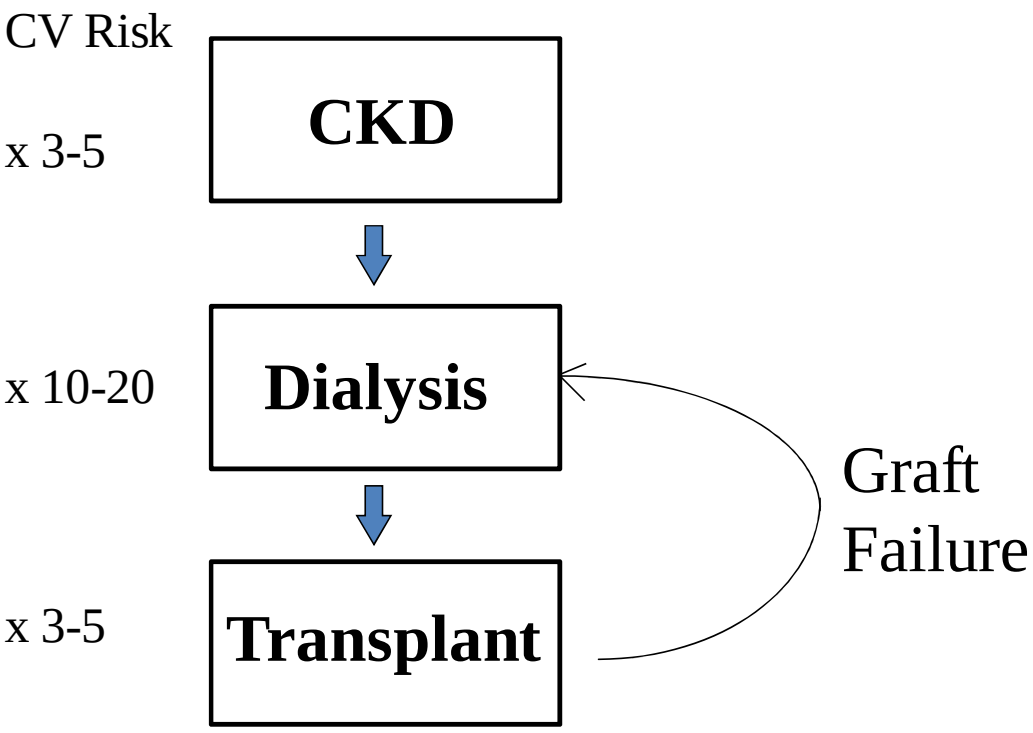
Introduction

During the latter part of the 20th century, better understanding of renal disease, dialysis techniques and renal transplantation have significantly improved prognosis of patients with end stage renal disease (ESRD). However, as survival has improved, other conditions have contributed significantly to the morbidity and mortality of ESRD patients. Cardiovascular (CV) disease, including cardiac arrest/arrhythmia, acute myocardial infarction (AMI), congestive heart failure and stroke, is the commonest cause of premature death in patients with ESRD. In addition, early stages of chronic kidney disease (CKD) have also been associated with poorer cardiovascular prognosis compared to the general population (1;2).

1.1 Progression and classification of chronic kidney disease

The natural history of patients with renal disease is shown in Figure 1.1. After a period of deteriorating renal function (which can last many years), some patients develop ESRD. These patients can receive dialysis in the form of haemodialysis (which is commonly in-hospital and thrice weekly) or peritoneal dialysis. Patients can receive a renal transplant just before requiring or, more commonly, whilst receiving dialysis. Patients with transplants which fail can return to dialysis until they are re-transplanted. Cardiovascular risk is higher than the general population at each stage of this disease process (Figure 1.1).

Figure 1.1 Natural history of patients with CKD and estimated increase in CV risk compared to the general population. Modified from (3).



To allow better evaluation and stratification of patients with renal dysfunction, the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines have classified CKD into 5 stages based on glomerular filtration rate (GFR) and evidence of kidney damage (by imaging, histology, or urinalysis). These have more recently been modified to include kidney transplant recipients and dialysis patients (Table 1.1). The main aim of implementing this system is to allow early recognition of kidney dysfunction and commence preventative measures to slow CKD and CV disease progression (2).

Table 1.1 Classification of CKD 2004 (2). GFR= glomerular filtration rate

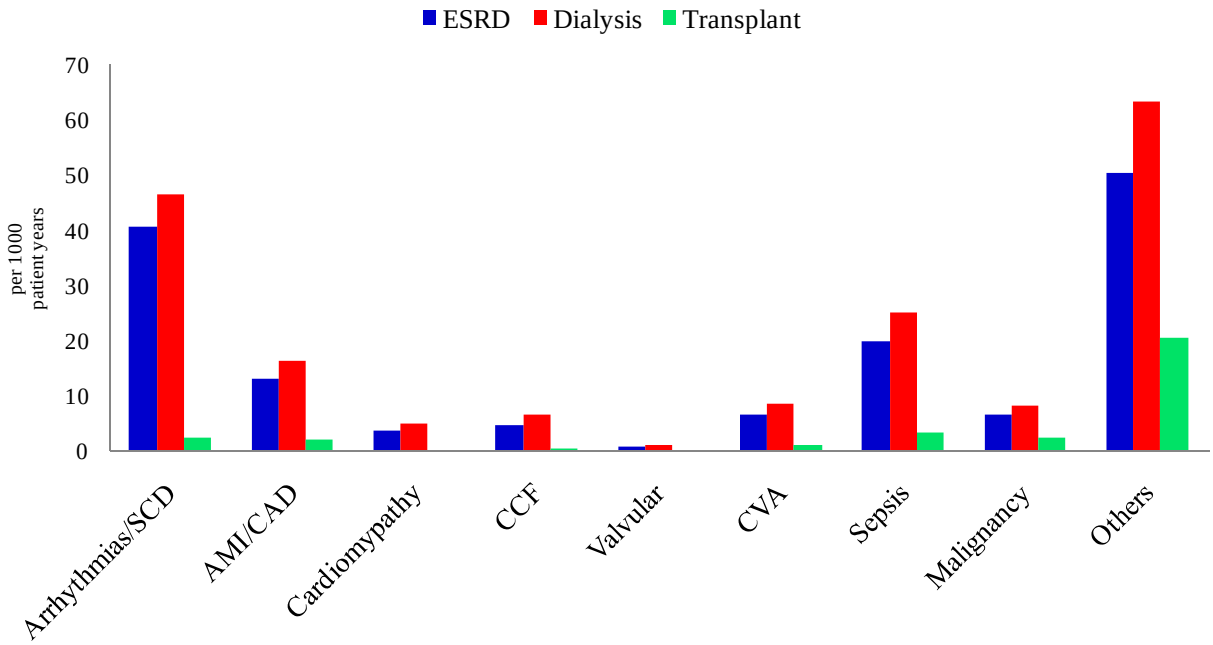
Stage	Description	GFR (ml/min/1.73m2)	Related Terms	Treatment
1	Damage with normal or ↑GFR	≥90	Albuminuria Haematuria Proteinuria	T if kidney transplant recipient
2	Damage with Mild ↓ GFR	60-89	Albuminuria Haematuria Proteinuria	
3	Moderate↓ GFR	30-59	Chronic renal insufficiency	
4	Severe ↓ GFR	15-29	Chronic renal insufficiency	
5	Kidney Failure	<15 or dialysis	Renal Failure,ESRD	D if receiving dialysis

1.2 Epidemiology of cardiovascular disease in ESRD patients

1.2.1 Prevalence of cardiovascular deaths in ESRD

According to data from the United States Renal Data System (USRDS), in 2008 annual mortality rates for ESRD patients and prevalent dialysis patients were 165.6 and 220.7 per 1000 patient-years respectively. Cardiac disease accounted for 41% of deaths in dialysis patients and 40% of deaths in ESRD patients (comprising all CKD 5 subjects: predialysis and dialysis). In dialysis patients 65.9% of cardiac deaths (26.9% of all deaths) were due to cardiac arrhythmia or sudden cardiac death representing the major cause of CV death (Figure 1.2). This pattern is also present in all ESRD patients (including peritoneal and pre-dialysis) and, to a lesser extent, in successfully transplanted patients (4).

Figure 1.2 Mortality rate by primary cause of mortality. (per 1000 patient years at risk, 2008).



Throughout all age groups CV risk is higher than the general population. Furthermore, increased relative risk of CV death is greatest in younger patients, who have a CV risk similar to elderly (70-80 years) non renal patients (5).

A significant problem of epidemiological studies from renal registries (both US and European) is defining the primary cause of death. In many cases autopsies are not performed, death certificates are not accurately completed, definitions used to define CV death tend to underestimate true cardiovascular deaths and it is often difficult to isolate a single cause of death in many patients. Nonetheless, these data demonstrate significant pathophysiological differences in CV death between the general population (where atherosclerosis and subsequent myocardial ischaemia and infarction are most common) and ESRD patients (where sudden, presumed arrhythmic death predominates CV mortality) (6).

1.2.2 Risk factors for CVD in ESRD patients

Large population based studies have identified a number of risk factors for CVD in the general population (Table 1.2). Furthermore large interventional studies have shown that modification of some of these risk factors improves CV survival. For example, lipid lowering using HMG Co-A reductase inhibitors has been shown to provide significant survival benefit for both primary and secondary prevention of CV events (7;8) and have been included in current clinical practice for many years.

In ESRD patients, premature cardiovascular death has been associated with higher prevalence of these “conventional” risk factors; but the relationship between these

risk factors and CVD is much less clear than in the general population. In addition, novel risk factors, which are often associated with the presence of uraemia, appear to have a more influential role on subsequent CV events than in the general population (Table 1.2). The majority of studies investigating CV risk factors in ESRD patients, have been performed in patients receiving regular haemodialysis, however many of these risk factors are also relevant to peritoneal dialysis or predialysis patients.

Table 1.2 Risk Factors for CVD in general population and ESRD patients (1;5)

Traditional CV Risk Factors- General Population	**Novel/ Uraemia Specific Risk Factors**
Advancing age	Haemodynamic/metabolic factors ESRD
Hypertension	Proteinuria
Dyslipidaemia	↑ Extracellular fluid volume
Diabetes Mellitus	Electrolyte imbalance/fluctuation
Sedentary Lifestyle	Vascular calcification
Previous IHD/CVA/PVD	Bone mineral disorders
Smoking	Homocysteine
Oxidative stress	Anaemia
LVH/LVSD	Inflammation
	Uraemic cardiomyopathy

1.2.2a Advancing age and gender

The mean age of patients commencing RRT has gradually increased over the last decade. Furthermore increasing age is commonly an independent predictor of mortality in most studies investigating associations with (CV) death. In all age groups male CKD patients have a significantly higher risk (x2.5) of acute myocardial infarction compared to female patients. However, female CKD patients have a 3-5x higher risk of acute myocardial infarction when compared to age and sex matched patients with no renal disease (5).

1.2.2b Hypertension

In the general population without co-existing CV disease, prospective observational studies have demonstrated that increments of 5-6mmHg in diastolic blood pressure (DBP) or 10mmHg systolic blood pressure (SBP) are associated with a 20-25% increased risk of ischaemic heart disease, 35-40% greater risk of stroke and 50% increased risk of heart failure (9). Furthermore, reduction of blood pressure reduces cardiovascular risk significantly (10). A number of large prospective trials have demonstrated that treatment with calcium channel blockers, diuretics, beta blockers and drugs affecting the renin- angiotensin system improve cardiovascular outcome in hypertensive patients (11-13).

Hypertension is very common in patients with CKD and is caused by a combination of reduced arterial compliance related to vascular calcification, endothelial dysfunction, fluid overload, and autonomic dysfunction (14). Furthermore, controlling blood pressure in patients with early stages of CKD has also been shown to slow progression of renal dysfunction and improve cardiovascular outcome

(15;16). However, similar prospective studies performed in dialysis patients have not consistently demonstrated a beneficial role for reducing blood pressure. Some studies have demonstrated that low and high blood pressure are associated with higher mortality.

- In a cohort study of 40933 haemodialysis patients followed for 15 months, pre dialysis systolic BP<110mm Hg and diastolic BP <50mmHg were associated with a hazard ratio for all cause mortality of 1.60 and 2.00 respectively (17).
- Similarly, an observational study in 16959 haemodialysis patients demonstrated that systolic BP< 120mmHg was associated with higher mortality after 1 and 2 years. However, after surviving 3 years on dialysis, higher systolic BP (>150mmHg) was associated with adverse prognosis suggesting that the relationship between blood pressure and survival may alter with time (18).

This "U" or "J" shaped relationship between blood pressure and mortality is most likely due to the association between hypotension and co-morbid conditions such as cardiac failure, diabetes mellitus, malnutrition and sepsis in dialysis patients,. As has been demonstrated in other studies involving chronic conditions (heart failure, advanced age), low blood pressure is associated with adverse outcome. This phenomenon is known as "reverse epidemiology" and has been demonstrated with other risk factors in ESRD patients (see below) (19).

There are few trials that have identified optimal targets and treatment for hypertension in ESRD patients. Promising studies have demonstrated that longer/more frequent dialysis may provide tight blood pressure control in

haemodialysis patients (20), however more studies are required to determine optimal targets and measures to control BP in patients receiving renal replacement therapy.

1.2.2c Dyslipidaemia

As renal dysfunction deteriorates there are complex disturbances in lipoprotein metabolism which are influenced by patient nutritional status, degree of renal dysfunction, presence of proteinuria, and diabetes mellitus. In patients with ESRD, plasma triglyceride levels are elevated and cholesterol levels may be high, normal or low dependent on nutritional status and modality of renal replacement. For example, patients on haemodialysis commonly have low total and low density lipoprotein (LDL) cholesterol. Peritoneal dialysis patients have elevated total and LDL cholesterol. In general, ESRD is associated with high levels of atherogenic particles (eg small dense LDL) independent of total or LDL cholesterol and reduced levels of atheroprotective high density lipoprotein (HDL) cholesterol.

As stated before, in the general population reduction of cholesterol using statins has been associated with primary and secondary prevention of CV events (7;8). In addition, the anti-inflammatory role of statins may contribute to their reduction in CV events. The JUPITER trial demonstrated that rosuvastatin reduced LDL-cholesterol and high sensitivity C reactive protein (CRP) levels. Whilst CV events and all cause mortality were significantly reduced in individual groups, the greatest reduction in events was found in the patients group that achieved both (21). In vitro studies have demonstrated that statins reduce inflammatory cell endothelium adhesion, alter smooth muscle cell behaviour in developing atheromas and aid stabilisation of atherogenic plaques (21;22).

The relationship between dyslipidemia and CV events/mortality in ESRD patients remains less clear. Data from renal registries suggest that, similar to hypertension, a "J" or "U" shaped relationship exists between serum cholesterol and survival in haemodialysis patients. As with blood pressure, this "reverse epidemiology" relates to high prevalence of malnutrition or other co-morbid conditions (inflammation) in patients with low levels of cholesterol. These data have contributed to the under usage of statins in dialysis patients, despite the high proportion of patients with diabetes and coronary heart disease (23;24).

Two randomised placebo controlled trials have failed to demonstrate significant reduction in CV events or death in haemodialysis patients treated with statins.

- The Deutsche Diabetes Dialyse Studie (4D) was a prospective randomised controlled trial investigating the effect of atorvastatin therapy on cardiovascular outcome in 1225 type 2 diabetic haemodialysis patients. Although LDL cholesterol was reduced (42% reduction), there was no statistical significant reduction of the composite primary endpoint (death from all cardiac causes, fatal stroke, non fatal MI, or non fatal stroke). Interestingly myocardial infarction events were reduced in the treatment arm. Post hoc analyses, however, revealed that adjudicated deaths due to coronary artery disease only accounted for 9% of deaths and sudden death accounted for 26% of all cause mortality (25).
- The AURORA trial was a prospective randomised study investigating therapy with rosuvastatin in 2776 haemodialysis patients. LDL cholesterol was reduced by 43% in the therapy arm but there was no significant effect on primary outcome (adjudicated death from cardiovascular causes, non fatal MI, non fatal stroke). In the

statin treated group, deaths from cardiovascular cause occurred at a rate of 7.2 events/100 patient-years compared to 7.3 events/100 patient–years in the placebo group (p=0.97) and death from definite coronary heart disease was not significantly different (26).

In both of these studies, the investigators postulated that lack of benefit in the treated cohort highlighted the difference between cardiovascular disease in patients with ESRD/diabetes and the general population. To explore the difference in cardiovascular disease in ESRD and the non-renal population, the results for placebo arms of the AURORA, 4D and 4S studies are shown in Table 1.3. The 4S study was a randomised placebo controlled study investigating the effect of simvastatin in patients who had proven coronary artery disease (8).

Table 1.3 Results from placebo arms of AURORA, 4D and 4S studies.

Study/ Cause of Death	AURORA % Placebo n=1378	4D % Placebo n=636	4S % Placebo n=2223
Study Population	**Haemodialysis**	**DM+ haemodialysis**	**Post AMI**
Cardiac Death	5.4	19.5	8.5
Non Fatal MI	2.5	11.8	16.9
Non- CV Death	8.1	28.5	3.0

These data show that patients receiving haemodialysis have a much higher risk of cardiac death than non fatal MI. However in a post MI, non dialysis-dependent cohort of patients, non fatal MI is the most prevalent CV event to occur; cardiac death is much less common. When we look at data from USRDS (see Figure 1.2) these haemodialysis patients are much more likely to suffer a cardiac arrhythmic death. The features that increase risk of sudden cardiac death/cardiac arrhythmia will be discussed later in this chapter.

1.2.2d Diabetes mellitus

According to UK Renal Registry and USRDS data, diabetes is the most common primary renal disease in patients receiving RRT and in the developed world diabetic nephropathy has become the most common cause of ESRD (between 20-35% of patients). In addition, the prevalence of diabetic patients with ESRD is rising which likely reflects improved survival of type 2 diabetic patients (27). Interestingly, recent reports from Finland and US suggest that the number of type 1 diabetic

patients requiring dialysis is decreasing possibly due to improved glycaemic, blood pressure and proteinuria control (28).

Diabetic patients who start dialysis have many CV risk factors including dyslipidaemia, hypertension, chronic inflammation and elevated oxidative stress leading to a poor prognosis on dialysis. Presence of diabetes at the start of dialysis is significantly associated with poorer survival, an independent risk factor for all cause and CV death, and it is estimated that cumulative risk for diabetes (2-3x compared to non diabetic ESRD patients) and presence of ESRD increases the overall risk of death to 50x that of the general non diabetic population (29). Accelerated coronary artery disease (CAD) is the greatest contributor to elevated CV morbidity and mortality in diabetic ESRD patients (30). In one study looking at 155 diabetic patients being assessed for renal transplantation (who are commonly positively selected due to their fitness to have a transplant), significant occlusion (>50%) in at least one vessel was found in 45% of patients despite 28% being asymptomatic of angina (31).

1.2.2e Cigarette smoking

Initial studies suggested that smoking had little effect on CV disease in ESRD patients and clinicians were reluctant to impose further restrictions on chronically unwell patients. However, two studies have demonstrated an association between smoking and CV disease similar to the general population.

- In an observational study investigating baseline CV risk factors and pre-existing disease in dialysis patients, smoking was independently associated with higher

relative risk of CV disease (32). In addition, a prospective study investigating development if CV events in a population of haemodialysis patients over 5 years showed that being a smoker at screening significantly increased risk of a subsequent CV events (33).

As a result of these and other studies, smoking cessation is encouraged in ESRD patients to improve CV survival.

1.2.2f Ischaemic heart disease

As stated above, sudden cardiac death and cardiac arrhythmia are the commonest cause of death in the ESRD population. Nonetheless, accelerated CAD and its sequelae account for almost 20% of CV deaths and is a significant feature of CV disease in ESRD patients. Cause of death classification is not always supported by post mortem evidence and it is likely that a significant proportion of deaths attributed as “arrhythmic” in origin are due to silent, undiagnosed CAD.

The classical triad to identify myocardial infarction: namely symptoms, ECG changes and myocardial enzyme elevation, can be misleading in this patient population making design of trials very difficult. Resting ECG abnormalities (particularly T wave and left ventricular axis changes) are common in ESRD patients and can be mistaken for ischaemia. In addition, significant myocardial ischaemia may be present in dialysis patients despite atypical or absent symptoms. Finally, myocardial enzymes such as troponin I and T may be elevated in renal impairment despite the absence of significant myocardial damage.

Nonetheless, several observational studies have highlighted elevated burden of CAD in ESRD patients. It has been estimated that in patients commencing dialysis, 30% of patients will experience AMI in the first year and 52% after the second (34). Furthermore, follow up data of these patients (35) has demonstrated poor prognosis in patients who suffered an MI with only 40% alive at 12 months and post-MI cardiac arrhythmias contributing to a very high in- hospital mortality (21% vs. 8% in the general population)

Poor post-MI prognosis may be due to under- or late diagnosis of MI at the time of presentation and delay in appropriate treatment. Even when patients with AMI are identified, a significantly lower number of patients are treated with thrombolytic therapy or referred for primary percutaneous intervention (PCI) compared to the non dialysis population. When discharged, these patients are under prescribed standard secondary preventative therapy: only 50-75% of patients receive aspirin, 22% receive β- blockers and 26% receive statin therapy (36). Reluctance to prescribe these drugs is presumably due to absence of evidence supporting their use in ESRD patients, who were commonly excluded from large studies for secondary prevention of CV events. However, a number of small observational studies have demonstrated significant benefit of treatment with aspirin, β- blockers or angiotensin converting enzymes in the 30 day post MI period compared to those not treated (37).

At the time of presentation, both thrombolytic therapy and primary PCI have been shown to significantly improve survival in ESRD patients. From USRDS data, Herzog et al showed that thrombolysis therapy for ST elevation MI was associated with a 28% relative risk reduction in all cause mortality at 48 months (38).

Furthermore, if the centre that patients present has access to primary PCI, ESRD patients should be treated similarly to the general population. In a large observational study of 4758 CKD patients who presented to hospital with acute coronary syndrome, Keeley et al demonstrated a significant improvement in long term mortality in patients with CKD 4-5 treated with primary PCI compared to medical therapy (39).

In dialysis patients with significant symptomatic CAD there is survival benefit of coronary artery bypass grafting (CABG) compared to PCI with angioplasty (± stent). Dialysis patients from the USRDS who received their first coronary revascularisation procedure between 1995 and 1998 were compared in a large retrospective study. All cause 2 year survival was significantly higher in patients who underwent CABG (56.4%) compared to PCI and PCI and stent groups (48.2% and 48.4% respectively; $p<0.01$). Multivariate survival analyses, demonstrated a 20% reduction in all cause mortality in patients treated with CABG and 6% reduction with PCI and stenting compared to PCI alone. However, the benefits of CABG over PCI need to be balanced with higher peri-operative complication rate of these procedures (8.6% for CABG vs. 6.4% for angioplasty and 4.1% for stenting) (35).

These studies suggest that coronary artery intervention is appropriate in the acute setting and/or in patients with critical coronary artery stenoses. In ESRD patients with less severe but flow limiting CAD, the role of coronary intervention is less clear due to a lack of prospective randomised controlled trials. In the CARP (asymptomatic patients undergoing high risk vascular surgery) and COURAGE studies (asymptomatic patients with stable CAD), PCI conferred no significant

survival benefit compared to patients treated with optimal medical therapy highlighting the need for careful selection of patients who undergo coronary revascularisation (40;41). At present, a prospective randomised controlled trial is planned in the US to determine the possible benefit of coronary revascularisation in ESRD patients.

1.2.2g Sedentary lifestyle

ESRD patients are at risk of physical deconditioning due to a number of reasons including large burden of co-morbidity (diabetes mellitus, peripheral vascular disease, CAD), recurrent hospital admissions, myopathy related to uraemia, hyperparathyroidism and anaemia. The UK Renal Association recommends regular exercise programmes for dialysis patients usually 3-5 times a week despite a lack of convincing evidence of benefit (42). Results from the Dialysis Morbidity and Mortality Wave 2 study demonstrated a significantly higher mortality in patients with severe limitations in physical activity. When different patient groups were exposed to varying levels of exercise, frequent exercise (4-5/week) was associated with improved survival (43).

1.2.2h Oxidative stress

Essential steps in development of atherosclerosis include perioxidation of membrane-bound, lipoprotein-associated fatty acids (in particular LDL- cholesterol) and oxidation of proteins by reactive oxygen species (ROS). Furthermore, ROS play a part in ischaemia-reperfusion injury during myocardial ischaemia/infarction. In the general population, interventional randomised trials have investigated the effect of antioxidants (e.g. acetylcysteine), which significantly reduce oxidation of LDL-

cholesterol and impair cellular response to oxidised LDL-cholesterol. Unfortunately, these studies have shown no significant clinical benefit (44).

A number of studies have demonstrated that patients receiving RRT (particularly haemodialysis) have higher levels of oxidative stress which may be amenable to intervention with antioxidant therapy. Although evidence is lacking, two small studies have demonstrated some benefit:

- In one study investigating 196 haemodialysis patients with known cardiac disease, treatment with oral vitamin E significantly reduced composite CV events during a median follow up of 519 days. However this study was limited by small numbers of patients and subsequent events (45). In a smaller randomised, placebo controlled study (n=134), acetylcysteine therapy was also associated with a lower all cause and CV mortality in haemodialysis patients (46).

Unfortunately, the use of these agents in ESRD patients has been limited by the absence of larger studies demonstrating a convincing clinical benefit.

1.2.2i Uraemic cardiomyopathy

Abnormalities of myocardial structure, detected by echocardiography, are very common (approximately 85%) in patients starting renal replacement therapy and are strongly associated with poorer outcome. These changes in myocardial architecture and function have been termed “uraemic cardiomyopathy”. Parfrey et al (47) studied 432 patients on initiation of dialysis and characterised three patterns of

cardiomyopathy: left ventricular hypertrophy (LVH), left ventricular systolic dysfunction (LVSD), and left ventricular dilatation (Table 1.4):

Table 1.4 Prevalence and survival of uraemic cardiomyopathy (47).

Abnormality	LV Hypertrophy	LV Dilation	LV Systolic Dysfunction	Normal
Prevalence (%)	**41**	**28**	**16**	**15**
Median Survival (months)	**48**	**56**	**38**	**66**

Only 15% of patients in this cohort had normal LV dimensions. On 2 year follow up, each abnormality was significantly associated with poorer survival compared to patients with normal echocardiograms after adjustment for age, and presence of diabetes and CAD. Additional data from USRDS have also demonstrated poorer survival in dialysis patients with LVH on echocardiogram (48).

LVH is the commonest abnormality of uraemic cardiomyopathy and a precursor for the development of other cardiac abnormalities. The development of LVH in ESRD patients will be discussed in detail in Chapter 3. Briefly, LV thickening is an adaptive process to:

- Increased pressure load leading to uniformly increased LV wall thickening with preservation of LV cavity size (concentric hypertrophy).

- Increased volume load causing LV dilatation and LV wall thickening to maintain wall stress. This leads to eccentric hypertrophy (49).

A number of factors associated with ESRD (e.g. anaemia, hyperparathyroidism) may also promote myocardial fibrosis in addition to sarcomere formation. Thus, the key histological features of uraemic cardiomyopathy which have been demonstrated in animal and patient biopsy studies are increased cardiomyocyte volume and interstitial myocardial fibrosis (50;51).

1.2.2j Anaemia

The presence of anaemia has been associated with significant morbidity and mortality in ESRD patients. Historically, anaemia has been associated with increased cardiac workload and subsequent development of LVH and LV dilatation in CKD patients. Despite observational studies demonstrating improved cardiovascular outcome, prospective randomised studies have failed to demonstrate significant reduction of LV mass or improved outcome in patients whose anaemia has been corrected. Furthermore, elevated haemoglobin levels have been associated with increased mortality in a number of prospective studies:

- In dialysis patients with cardiac disease treated with erythropoietin, the Normal Hematocrit Study (NHS) was stopped early due to a trend toward poorer outcome in the high haematocrit compared to the low haematocrit group (52). Furthermore, Foley et al demonstrated no difference in LV mass of dialysis patients treated with erythropoietin to achieve full or partial correction of haemoglobin levels (53).

- In pre-dialysis patients, two randomised prospective studies (CHOIR and CREATE) have demonstrated poorer cardiovascular outcome and/or higher mortality in patient groups treated with erythropoietin to achieve higher haemoglobin levels (54;55).

Given that patients with lower haemoglobin include those with more comorbidities, including ongoing inflammation and malnutrition, it is not surprising that anaemia is associated with poorer survival in ESRD patients. However, optimum level of haemoglobin and time of commencement of erythropoietin therapy remain controversial. The relationship between anaemia and features of uraemic cardiomyopathy will be discussed in further detail in Chapter 3.

1.2.2k Proteinuria

Proteinuria is defined as urinary protein excretion greater than 300mg over 24 hours. A number of observational studies have demonstrated that proteinuria is an independent risk factor for all cause and cardiovascular mortality in patients with and without diabetes mellitus:

- Post hoc analyses of the RENAAL (Reduction in Endpoint in Non-insulin dependent diabetes mellitus patients with the Angiotensin II Antagonist Losartan) trial showed that proteinuria>3g/24 hours was associated with doubling of serum creatinine or ESRD in 85% and cardiovascular morbidity or mortality in 44% of patients. These endpoint rates were significantly higher compared to patients with proteinuria <1.5g/24hours (28% and 29% respectively) (56).
- In a 16 year study of non diabetics of the Framingham cohort, evidence of significant proteinuria (>2+ on dipstix) increased mortality threefold (57).

- Tonelli et al (58) demonstrated in patients with ischaemic heart disease, that those with reduced eGFR or dipstick urinalysis positive proteinuria (≥1+) were at highest risk of dying from a CV event compared to those without these risk factors. Furthermore, those subjects with both had the worse survival and highest CV event rate.

These and other studies support a significant association between presence of proteinuria and CV events or death in diabetic and non diabetic patients. The link between proteinuria and CV risk in CKD patients is multi-factorial and felt to represent pathophysiological associations rather than a causal relationship. These factors include:

- Extracellular volume overload
- Hypertension and activation of the renin angiotensin aldosterone system
- Vascular calcification
- Endothelial dysfunction/oxidative stress

1.2.2l Bone mineral disorders and vascular calcification

As renal function deteriorates, chronic hyperphosphataemia and hypocalcaemia cause secondary and occasionally tertiary hyperparathyroidism. Disturbances of calcium and phosphate homeostasis have been reported as early as CKD stage 3 and a number of large observational studies have identified serum markers of bone mineral disorders as risk factors of poor outcome:

- Data from the USRDS demonstrated that hyperphosphataemia and calcium-phosphate product were strong independent predictors of mortality in 7096

haemodialysis patients when corrected for age, sex, race, smoking status, and presence of diabetes mellitus or neoplasm. Elevated serum PTH was also associated with death (59).

- Hyperparathyroidism not only increases risk of fractures, but also has adverse effects on all cause and cardiovascular mortality. In a much larger US dialysis study, moderate to severe hyperparathyroidism (PTH>600pg/ml) was independently associated with mortality, CV hospitalisation and fracture when corrected for age, sex, race, diabetes and dialysis vintage (60). PTH has been associated with adverse cardiovascular outcome due to its effects demonstrated in vitro. PTH specific receptors present on myocardial and vascular cells isolated from rat perfusion models, have demonstrated positive inotropic and chronotropic effects due to altered intracellular calcium handling when stimulated. Furthermore in vitro effects of elevated PTH (as in patients with CKD) demonstrate stimulation of cardiac fibroblasts to produce collagen type 1 with subsequent interstitial fibrosis (61).

The development of vascular calcification (VC) has been associated with increased cardiovascular morbidity and mortality. Vascular calcification is associated with calcium deposition within the medial and intimal layers of arterial walls. Medial deposition, which is very common in dialysis patients, results in reduced arterial compliance, widened pulse pressure, decreased coronary perfusion, and associated autonomic and endothelial dysfunction. Intimal deposition, which can also occur in patients with normal renal function, is associated with atherosclerotic plaques, subsequent myocardial infarction and other thrombotic events. Intimal layers of cardiac valves can also be affected leading to significant aortic and mitral valve stenosis. In patients with CKD, VC is commonly localised to coronary, aortic and

ileo-femoral vascular regions and can be detected using plain X rays and computed tomography (usually electron beam; EBCT). Vascular calcification can be observed in young dialysis patients and its presence and extent are strong predictors of CV and all cause mortality:

- In a prospective study of 110 dialysis patients, Blacher et al measured VC using ultrasonography and scored patients according to presence of VC at different sites. Each increase in 1 unit score was independently associated with all cause and CV mortality (62).
- Using EBCT to prospectively assess 101 dialysis patients, Matsuoka et al demonstrated that all cause and CV mortality was higher in patients with evidence of coronary artery calcification (63).

Although bone mineral disorders are associated with development of VC, most investigators do not believe that this is merely due to precipitation of calcium and phosphate within vessel walls. In vitro studies have demonstrated transformation of vascular smooth muscle cells to osteoblasts mediated by phosphate, calcium and other osteogenic protein such as ostecalcin, ostenectin, alkaline phosphatase, and collagen type 1. This is also associated with reduced serum levels of VC inhibitors such as Gla-protein, fetuin- A and ostepontin in ESRD patients (64). In CKD patients the reason for alteration in vessel wall activity remains unclear and is an area of intense research interest.

1.2.2m Inflammation and C- reactive protein

In the general population, the presence of a chronic inflammatory process has been implicated as an important contributor to atherogenesis and plaque rupture. A number of studies have demonstrated C-reactive protein (CRP), which is an acute phase reactant produced by hepatocytes in response to interleukin-1 and 6 (IL-1, IL-6) and tumour necrosis factor alpha (TNFα), as a predictor of adverse cardiovascular outcomes. Whether CRP is a non-specific marker of an ongoing inflammatory response or directly involved in the atherogenic process remains unclear. Nonetheless, presence of elevated CRP is a marker of poor primary and secondary CV outcome in the general population:

- In a Danish study of over 50000 individuals in whom high sensitivity CRP (hs-CRP) was measured, CRP>3mg/L was associated increased risk of ischaemic heart disease (RR1.6) and stroke (RR 1.3) compared to patients with CRP<1mg/L (65).
- In patients with ischaemic heart disease, elevated CRP measured 12-24 hours post acute coronary syndrome (n=448) was associated with a significantly higher 30-day mortality, greater infarct size and higher risk of subsequent heart failure (66).
- In a case control study of 22071 healthy male physicians who had a single measurement of CRP and were followed for 17 years, baseline CRP was significantly associated with sudden cardiac death. In addition, individuals with CRP in the highest quartile had the highest risk of sudden cardiac death (RR 2.78) compared to the lowest quartile (67).

Patients with ESRD are in a state of chronic inflammation and various studies have demonstrated inflammatory biomarkers such as CRP, IL-6 and TNF α as

independent predictors of CV mortality. In addition, hypoalbuminaemia often accompanies chronic inflammation and is also associated with adverse outcome:

- In 224 maintenance dialysis patients, elevated CRP concentrations measured at study recruitment were significantly associated with poorer survival and independently predicted death when adjusted for age, sex race, dialysis vintage, smoking and cardiac history, and dialysis adequacy (68).
- In a prospective study of 176 ESRD patients, lower serum albumin and elevated IL-6 independently predicted development of CV morbidity and all cause mortality over a follow up of 26 months (69).

As in the general population, it is unclear whether these pro-inflammatory proteins are directly involved in initiation and progression of atherosclerosis in CKD/ dialysis patients or are markers of ongoing atheromatous formation, endothelial dysfunction, vascular calcification and insulin resistance. In vitro evidence suggests IL-6 and TNFα directly stimulate endothelial cells to promote atherogenesis by increasing monocyte adhesion, smooth muscle proliferation and LDL-oxidation (69).

1.2.2.n Haemodynamic instability during haemodialysis

Intermittent haemodialysis (HD), particularly when large volumes of ultrafiltration are attempted, exerts significant haemodynamic imbalance and it is estimated that approximately 25% of patients develop episodes of intradialytic hypotension (IDH) (70). Patients receiving haemodialysis are also susceptible to myocardial ischaemia, as discussed above, due to:

- Large vessel epicardial CAD
- Micro-coronary artery occlusion and myocyte- capillary circulatory mismatch associated with LVH
- Impaired diastolic coronary blood flow due to reduced vascular compliance.

ECG studies have demonstrated the presence of asymptomatic ST segment changes during HD at rates between 15-40%. More recently, intradialytic LV functional analyses using echocardiography or cardiac positronic emission tomography, have demonstrated development of myocardial wall stunning during HD, usually in the absence of symptoms. These abnormalities develop in the absence of significant CAD or cardiovascular disease. In a small study (n=70) of HD patients assessed during dialysis, intradialytic hypotension and volume of ultrafiltration were independent predictors of myocardial stunning. After 1 year follow up, presence of intradialytic myocardial stunning was associated with higher mortality and poorer LV function compared to those with no intradialytic LV changes (71).

Promising measures to reduce myocardial stunning during dialysis have been pursued including reduced temperature dialysis (35°C instead of 37°C) and biofeedback dialysis (BFD) which reduces ultrafiltration rates in response to small changes in blood pressure (72;73). Both techniques significantly reduce IDH and are associated with reduced RWMA number. The effect that these measures have on long term outcomes is awaited.

1.3 Sudden cardiac death in ESRD patients

As previously discussed, CV disease in ESRD patients differs from the general population. The predominant cause of death in ESRD patients is cardiac arrest or cardiac arrhythmia (Figure 1.1), as opposed to complications of coronary atherosclerotic disease which accounts for most deaths in the non-renal disease population. Event rates for SCD in the general non-renal population have been estimated at 1.89/ 1000 patient years, in contrast to ESRD rates of 48 per 1000 patient years and dialysis rates of 60 per 1000 patient years (74). Treatment of risk factors (e.g. dyslipidaemia, hypertension) which have been shown to reduce CV morbidity and mortality in the general population, has little, if any effect on ESRD patients suggesting that pathogenesis is inherently different.

1.3.1 Definition

Various criteria have been employed to define SCD. For the purposes of this thesis sudden cardiac death is defined as an unexpected death of cardiac aetiology, which occurs within one hour from the start of any cardiac-related symptoms due to cardiac arrest or arrhythmia. These deaths are commonly due to ventricular arrhythmias, namely ventricular tachycardia (VT) or fibrillation (VF). Although SCD can occur in patients with structurally normal hearts, it is more common in patients with underlying myocardial structural abnormalities such as hypertrophic cardiomyopathy, or less commonly LVH.

In general terms, development of a fatal cardiac arrhythmia requires abnormal "substrate" (e.g. LVH, cardiomyopathy) interacting with a "triggering mechanism"

(e.g. ischaemia, hyperkalaemia). Both substrate and triggers are common in ESRD patients.

Sustained VT has been studied extensively in post MI patients and occurs due to slowed cardiac action potential (AP) propagation between areas of ventricular scarring, followed by re-entry into excitable, viable myocardium. As a result a rapid ventricular circuit is established. In patients with reduced LV function, rapid ventricular rate results in significant haemodynamic compromise (75). Whether VT directly leads to SCD or more life threatening cardiac arrhythmias remains debatable, however the presence of sustained VT on 24 hour ECG (from ICD monitoring) has been significantly associated with SCD (76). The development of VF is not as well understood and usually requires more diffuse underlying cardiac disease. Currently, VF is thought to be due to multiple small regions of disorganised re-entry resulting in abnormal depolarisation fronts and dispersion of ventricular repolarisation. Since there is no ordered ventricular depolarisation, there is no co-ordinated contraction resulting in failure to generate adequate cardiac output (77).

1.3.2 Epidemiology of sudden cardiac death in ESRD patients

Data from the US demonstrate the huge impact on mortality of SCD in ESRD patients. Sudden cardiac death is the commonest cause of death in all ESRD patients accounting for 20-30% of all deaths. Similar rates are seen for dialysis (haemo- and peritoneal) patients. These figures are similar to rates of sudden cardiac deaths (25-30%) reported in the HEMO and 4D trials (25;78).

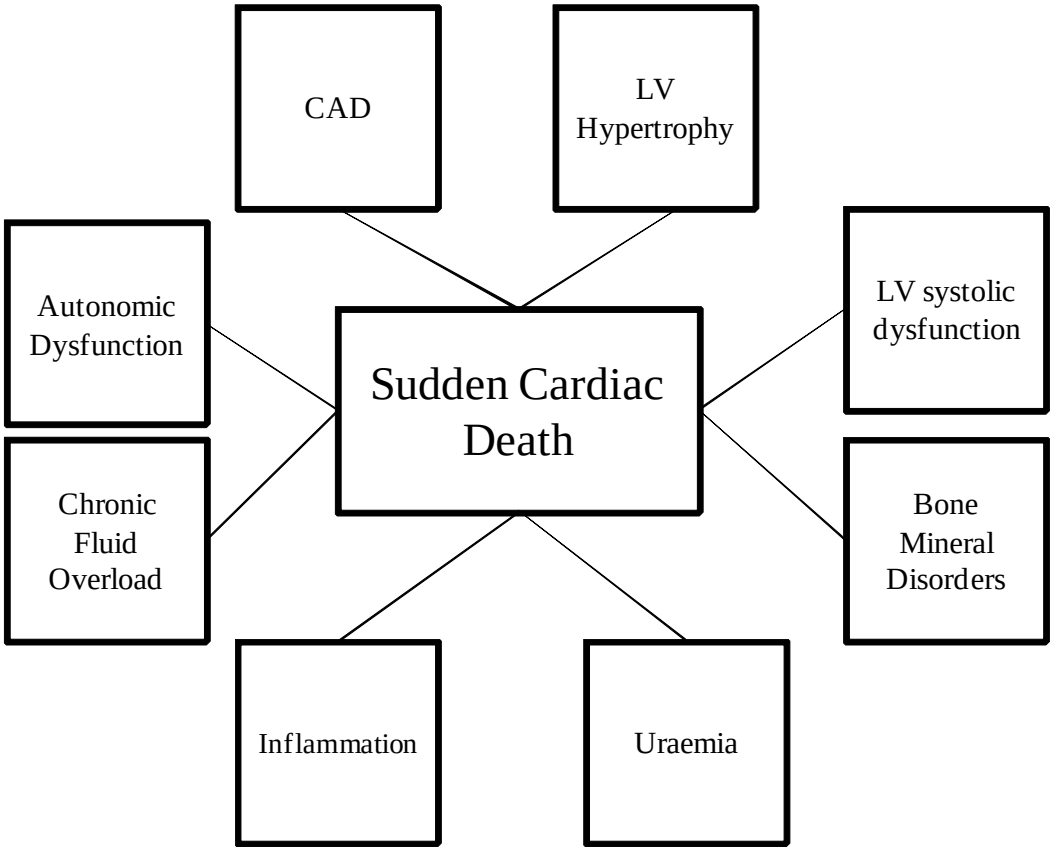
The risk of SCD after initiation of dialysis increases with dialysis vintage. In a retrospective study of incident dialysis patients from the US who had survived at

least 1 year after dialysis initiation, event rate rose from 93 per 1000 patient years at 2 years to 164 per 1000 patient years after 5 years from dialysis initiation. Comparison of dialysis modality reveals that in the first 3 months of dialysis, patients receiving haemodialysis have a 50% higher risk of SCD compared to peritoneal dialysis patients. However after 18 months, event rates are similar and by 36 months peritoneal dialysis are higher by less than 10% (79;80).

1.3.3 Aetiology of sudden cardiac death in ESRD patients

Section 1.2 has described many of the risk factors commonly associated with CV disease in ESRD patients. However, high prevalence of these risk factors in ESRD patients only partially accounts for elevated risk of SCD. Figure 1.3 highlights some of the features associated with SCD in ESRD patients. In particular, factors which promote changes in myocardial structure (substrate) or cardiac environment (triggers) have been implicated (81).

Figure 1.3 Factors associated with SCD in ESRD patients. CAD= coronary artery disease. Modified from (81).



1.3.3a Uraemic cardiomyopathy and sudden cardiac death

Myocardial structural changes associated with uraemic cardiomyopathy (described in section 1.2.2i) have been associated with sudden cardiac death. In post MI populations, LV systolic dysfunction is the greatest predictor of sudden cardiac death and has been used as the most important factor to determine primary prevention of cardiac arrest in this patient population:

- The Multicenter Automatic Defibrillator Implantation Trial (MADIT II) recruited 1232 post MI patients with reduced LV ejection fraction (LVEF<30%) on echocardiography. Patients were assigned to receive implantable cardioverter defibrillator (ICD) or conventional therapy. Patients in the ICD arm had a significantly lower mortality rate (14.2% ICD vs 19.8% conventional medical therapy, p=0.016) (82)
- The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) assigned 2521 patients with symptomatic heart failure (from ischaemic and non-ischaemic causes) and LVEF less than 35% to conventional therapy, conventional therapy and amiodarone or conventional therapy and ICD. Mortality rate was significantly lower in the ICD group (22% ICD, 28% medical therapy with amiodarone, 29% medical therapy without amiodarone). ICD therapy was associated with a 23% relative reduction in risk of death and absolute reduction in mortality of 7.2% after 5 years compared to the medical therapy without amiodarone group (83).

Both of these studies have been instrumental in American College of Cardiology/American Heart Association (ACC/AHA) guidelines stating that ICD insertion should be considered in patients with “LVEF less than or equal to 35% and

mild to moderate symptoms of heart failure and in whom survival with good functional capacity is otherwise anticipated to extend beyond 1 year" (84).

Unfortunately, patients with ESRD were excluded from these trials. Severe LV systolic dysfunction has been reported to be present in 15-20% of ESRD patients, and has not been demonstrated as a significant predictor of SCD.

- A retrospective analysis of dialysis patients in the US who died of sudden cardiac death, showed that 71% had normal or only mild-moderate LV dysfunction on echocardiogram (85). Furthermore, Genovesi et al demonstrated that LVEF <40% was not a significant predictor of SCD in ESRD patients (86).

Left ventricular hypertrophy has been associated with SCD in patients with hypertension and ischaemic heart disease. The Framingham Study demonstrated a 5 fold increase risk in men and 3 fold increase risk in woman of SCD in patients with LVH on ECG compared to those with normal resting ECG (87). LVH is believed to increase risk of ventricular arrhythmias and SCD due to a number of factors:

- Microvascular ischaemia- reduced subendocardial blood flow due to elevated diastolic blood pressure, inadequate capillary angiogenesis (causing myocyte-capillary mismatch) and increased oxygen requirement due to elevated wall tension result in ventricular ischaemia.
- Electrophysiological changes- irregular myofibril architecture and fibrosis may partially impede AP propagation leading to non uniform ventricular de- and repolarisation.

- Abnormalities of hypertrophied myocyte- cellular changes tend to increase arrhythmogenic properties including alteration in intercalated disc spaces involved in cell to cell AP propagation and changes in transverse tubule system which communicate between surface cell membrane and the sarcomere. It remains unclear if these changes in structure are related to specific structural changes.
- External pressure- cardiac myocytes respond to external pressure (eg increased wall tension) via stretch activated channels which stimulate cytoplasmic ionic changes and lower AP excitation threshold.

As stated before, LVH is very common (60-80%) in ESRD patients and is associated with sudden cardiac death in dialysis patients, independent of blood pressure:

- Post hoc analyses of the 4D study demonstrated that in 1253 patients, those with ECG evidence of LVH had a 60% increased risk of SCD after 4 years (88).
- Poaletti et al demonstrated that worsening of LVH on echocardiogram (per $1g/m^2$) independently predicted SCD in haemodialysis patients followed for 10 years (89).

It should be noted that in these and other studies, presence of LVH has been demonstrated using ECG criteria or M-mode echocardiography. As will be discussed, these techniques are inaccurate when estimating LV mass, particularly in ESRD patients.

1.3.3b Coronary artery disease and sudden cardiac death

As previously discussed, accelerated CAD is common in patients with ESRD and accounts for a significant proportion of CV morbidity. As in the general population, it is likely that CAD also contributes, albeit not as significantly, to SCD. This has been highlighted in a study in patients with ESRD and significant occlusive coronary disease. Despite revascularisation, subsequent annual mortality due to arrhythmic deaths was considerably higher than non-renal populations (8.5% and 7% after PCI and stenting and CABG respectively) suggesting that improving coronary blood flow may not reduce risk of SCD and alternative factors may play an important role (90). Furthermore, agents that modify established risk factors for CAD in non renal patients (e.g. dyslipidaemia) have not altered CV outcome of ESRD patients.

1.3.3c Electrolyte fluctuation and hyperkalaemia

Due to the non-physiological and intermittent nature of maintenance HD, rapid electrolyte shifts and hyperkalaemia (due to accumulation of potassium) increase risk of cardiac arrhythmias. This elevated risk is unsurprising given the significant electrolyte imbalance present immediately before HD and the haemodynamic stress produced during an HD session. These changes are reflected in many studies investigating the temporal risk of SCD in maintenance HD patients which have shown that risk is highest immediately before and after the first weekly HD session. One study reported a 3-fold increase in risk of sudden death in the immediate 12 hours before the end of the long weekend and a 1.7-fold increased risk of SCD in the 12 hours from the start of dialysis after the long weekend (85;91). As expected elevation of serum potassium, which is highest just before the start of dialysis, was

shown to be an independent risk factor for SCD in HD patients (K+>6mmol/l; RR 2.74).

1.3.3d Autonomic dysfunction

Autonomic dysfunction, resulting in enhanced sympathetic activity, has been associated with SCD in post MI and heart failure patients. Furthermore, autonomic function in ESRD patients is characterised by sympathetic over activity:

- In one study, sympathetic nerve discharge was higher in HD patient compared to normal controls. Interestingly sympathetic activity in HD patients with bilateral nephrectomies was similar to controls, leading the investigators to believe that autonomic imbalance arose from the failing kidneys (92).
- In a prospective study of 228 HD patients, plasma norephinephrine level was elevated compared to previously published levels and significantly associated with adverse outcome and CV events (93).

Thus it is likely that autonomic dysfunction may play a role in promoting cardiac arrhythmias in ESRD patients.

1.3.3e Factors promoting myocardial fibrosis

As stated above, the creation of a non-uniform wavefront of myocyte de- and repolarisation promotes the development of VTA. Due to differences in action potential conductivity between myocyte plasma membrane and collagen fibres, myocardial fibrosis promotes VTA formation (94). Post mortem endomyocardial biopsies of ESRD and renal transplant patients have demonstrated significantly

elevated levels of interstitial fibrosis compared to non diabetic, non hypertensive controls. In these studies, severity of fibrosis was correlated with dialysis vintage and was demonstrable years after renal transplantation (51).

A number of animal models have isolated humoral and mechanical factors, some of which have previously been discussed, that may promote cardiac fibrosis in uraemic patients including fluid overload, oxidative stress, inflammation with excess of cytokines such as cardiotrophin-1 and transforming growth factor β (TGFβ), hyperphosphataemia, hyperparathyroidism, anaemia, vitamin D deficiency and other uraemic "toxins" yet to be identified (95;96).

1.3.4 Identification of the ESRD patient at risk of SCD

Identification of patients at high risk is desirable in order to implement prophylactic measures to reduce the rate of SCD in ESRD patients. However, this remains very difficult due to the multifactorial nature of SCD within this patient group. If criteria from the heart failure population are applied to ESRD patient (i.e. reduced LVEF) we will not only expose patients to an invasive procedure (ICD insertion) without adequate evidence from prospective trials, but also potentially omit patients that may be at risk (as mentioned above LVSD has been noted to be present in only 15% of patients).

In heart failure/post MI patients, reduced LVEF alone has been shown to have low sensitivity and specificity for predicting SCD. As an adjunct, electrophysiological (EP) tests have been evaluated to identify heart failure patients at higher risk of SCD and reduce the number of unused ICDs. It is estimated, based on reduced LVEF

alone, almost 18 ICDs need to be implanted to save one life in the post MI population Furthermore, in early primary prevention trials, EP tests involved invasive direct cardiac stimulation to induce VT, however more recently non invasive techniques have been evaluated (97;98). Evidence is absent for the use of EP tests (both invasive and non-invasive) for prospectively assessing risk of cardiac arrhythmia in ESRD patients since these patients were excluded from initial prospective studies using SCD as the primary endpoint. Some studies have attempted to identify high risk ESRD patients.

1.3.4a Ambulatory electrocardiography

Presence of non sustained VT (defined as 3 or more consecutive beats of ventricular origin with a rate >120bpm and lasting greater than 30s) with structural heart disease or complex ventricular premature beats (R on T, runs of 2 or more, multiform or bigeminal beats) in patients post MI has been demonstrated to increase risk of SCD 2 to 5- fold compared to patients without such arrhythmias (99;100).

In patients with ESRD, ventricular arrhythmias are commonly observed on ambulatory ECG especially during and immediately after HD sessions when there are significant changes in patient electrolyte and haemodynamic status (101). However the role of ventricular arrhythmias detected by ambulatory monitoring for predicting future arrhythmic events is not well established in ESRD patients.

1.3.4b Microvolt T wave alternans

Beat to beat variation in ECG wave amplitude and shape has been observed for over a century. Specifically, T wave alternans (TWA) is defined as fluctuations in T

wave shape or amplitude and macroscopic TWA has anecdotally associated with onset of VTA, especially VF, in a variety of clinical situations including MI, electrolyte derangements, and long QT syndrome (102).

At both cellular and tissue level, TWA has been shown to be closely associated with repolarisation alternans (RA) which describes regular variation between two patterns of ventricular repolarisation on an every-other- beat basis, each with a constant cycle length. Repolarisation alternans is thought to underlie development of TWA. Pastore et al used optical mapping of the guinea pig heart to demonstrate that with increasing atrial pacing, TWA developed on surface ECG with the development of RA at the level of the cardiomyocyte (103). Magnitude of RA is much larger than corresponding 12-lead ECG TWA and development of ECG digital processing has allowed very small (at the microvolt level) changes in T wave amplitude and morphology (called Microvolt T Wave alternans: MTWA) to be quantified. It is important to appreciate that RA is a physiological rate dependent property of cardiomyocytes that develops during tachycardia in structurally normal heart, but develops at much lower heart rates in diseased hearts.

The cellular basis of RA is the focus of intense experimental study and remains controversial, but aims to provide insight into the arrhythmogenic state of different cardiac conditions. Briefly, generation of RA is believed to be due to action potential duration alternans (whereby premature stimulation of myocytes that have altered properties greatly affect their diastolic/refractory interval and thus affects subsequent action potential duration) and abnormal handling of intracellular Ca^{2+} (termed calcium transient alternans) (104). Presence of RA is thought to produce

arrhythmogenicity due to development of discordant RA between neighbouring cardiomyocytes. Normally, RA develops in a uniform (concordant) fashion that ensures all myocytes alternate in phase (long-short-long). However, at elevated heart rates or after ventricular ectopy, some myocytes move out of phase, resulting in discordant alternans between adjacent cardiomyocytes (long-short vs short-long) thus increasing the chance that a cardiomyocyte will attempt to conduct AP to a neighbouring cell in a refractory state. This amplifies any non-uniformity in ventricular repolarisation and increases risk of VF in structurally normal heart and VT or torsades de pointes in abnormal hearts.

Initial clinical studies of MTWA during invasive atrial pacing demonstrated an increase risk of VTA. MTWA is currently performed during exercise using commercially available systems (CH2000 or HearTwave II, Cambridge Heart, Bedford, MA). Exercise ECGs are digitally acquired at stable heart rate and aligned according to the start of the QRS complex, allowing measurement of T wave amplitude. Spectral analyses are performed to quantify fluctuations in alternate beat T wave size. Fast Fourier transformation, a computer mathematical modelling system to quantify variations in frequency for continuous variables, is performed and T wave alternans is said to be present and result classified according to established electrophysiological criteria. Tests are classified as positive, negative or indeterminate by the commercial system and for clinical purposes as negative or non-negative/abnormal (positive or indeterminate result) depending on the study. More details for classification of tests are provided in Section 2.6. Presence of atrial fibrillation does not allow MTWA testing as unequal R-R wave intervals interfere with frequency analysis.

Initial studies showing a significant association between MTWA result and SCD were performed in high risk post-MI patients with reduced LVEF. More recent studies assessing the use of MTWA for primary prophylactic ICD insertion have shown improved efficiency for intervention:

- In a prospective US study of 549 patients with reduced LVEF, 49% of patients had documented CAD and an abnormal MTWA result was an independent predictor (HR 6.5) of the primary end point of all cause mortality and non sustained VT after 2 years (105).
- Similarly, Chow et al demonstrated in 768 patients with ischaemic cardiomyopathy and LVEF<35%, that an abnormal MTWA result was a significant predictor of all cause and arrhythmic mortality (HR 2.24 and 2.29 respectively) (106).
- The Alternans Before Cardioverter Defibrillator (ABCD) trial was the first study to use MTWA to guide prophylactic insertion ICD insertion. 566 patients were recruited with ischaemic cardiomyopathy and documented non sustained VT. Patients underwent EP studies or MTWA testing and ICDs were inserted if tests were positive. One year survival showed that positive and negative predictive values for MTWA results were comparable to more invasive EP studies. Furthermore primary end point (ICD discharge or SCD) event rates were similar after 1 year. Interestingly, predictive values were much better if patients had positive EP and MTWA tests suggesting that these tests were complementary (107).

These studies have suggested that MTWA may improve the inefficient practice of ICD insertion based on reduced LVEF alone. Most studies estimate that MTWA

testing may improve efficiency of number needs to treat to save one life from 18 to 9 103:104).

Two more recent studies have suggested that the predictive value of MTWA may not be as encouraging as initial studies suggested:

- The MASTER I (Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients) failed to demonstrate an increase in ICD detected VTAs in patients with abnormal MTWA result. However in this study, abnormal MTWA test independently predicted death (108;109).
- A MTWA sub study (n=490) of the SCD-HeFT demonstrated no significant predictive value of an abnormal MTWA result for VTA's or mortality after 14 months. However in the original study the survival curves did not begin to separate until 14 months in favour of ICD group suggesting that the MTWA sub study may have been stopped too early (110).

Nonetheless, these two large trials have cast doubt on the usefulness of MTWA in heart failure patients. Some investigators believe that MTWA should only be part of risk stratification process which also includes assessment of LV function and possible EP testing.

There have been very few studies investigating other groups at risk of SCD. In type 2 diabetics without evidence of CV disease, abnormal result was found in 25.4% of patients compared to only 5.7% in healthy age and sex matched controls (111). Similarly, in athletes with previous evidence of VTA (ventricular ectopics or NSVT)

referred for EP studies, abnormal MTWA was detected in 32% of subjects and there was significant correlation between EP studies and MTWA results (112).

Only one small (n=9) study has been performed in HD patients immediately before and after an HD session. This study demonstrated that the number of patients with an abnormal MTWA result increased immediately after an HD session (113).

1.3.4c QT dispersion

QT dispersion has emerged in recent years as another non-invasive method of predicting development of ventricular arrhythmias. QT dispersion is defined as the difference between the shortest and the longest heart rate corrected QT interval on a standard 12 lead ECG; it represents variation in ventricular repolarisation (like MTWA) and predisposition to ventricular tachyarrhythmias. As with MTWA, a wide QT dispersion (above 65-74ms) has been shown to be a risk factor for cardiac arrhythmia in patients starting dialysis, with biventricular cardiac failure after myocardial infarction and drug induced VTAs (114;115).

A study in haemodialysis patients measured QT dispersion over a single haemodialysis session. Compared to healthy individuals, QT dispersion was significantly higher in haemodialysis patients (63.1 +/- 20.6ms before haemodialysis vs 36.0 +/- 13.7ms in controls). After haemodialysis, QT dispersion rose to levels measured in post MI patients suggesting that haemodialysis patients are at greater risk of arrhythmias and sudden death in the post dialysis period (101). There has been ambivalence among cardiac electrophysiologists regarding the relevance of QTD predicting risk of arrhythmia in high risk groups (eg.post myocardial

infarction). However a considerable amount of literature supports its use and this technique has not been completely evaluated within the ESRD group.

1.3.4d Heart rate variability

As mentioned above, autonomic dysfunction is associated with SCD in ESRD patients. Heart rate variability (HRV) measures autonomic influence on the heart by quantifying R-R intervals or heart rate changes over a specified number of cardiac cycles. The commonest way to assess HRV uses ambulatory ECG to determine time and frequency domain measurements. Time domains provide continuous measurements of R-R intervals, whilst frequency domains estimates changes in heart rate as a frequency function using fast Fourier transformation.

In healthy individuals HRV is high due to respiration (parasympathetic control) and higher values are associated with a functionally efficient autonomic nervous system. However, reduced HRV independently predicts mortality and SCD in patients with underlying CV disease and healthy controls (116). Studies measuring HRV in dialysis populations have demonstrated reduced heart rate variation as an independent predictor of all cause or CV mortality.

- Oikawa et al assessed 383 HD patients and demonstrated that decreased HRV on ambulatory ECG monitoring was an independent predictor of CV death adjusting for the presence of diabetes mellitus. A similar study (n=196) has also shown decreased HRV as a predictor of SCD in dialysis patients(117;118).

In these studies the ratio of low frequency (indicating sympathetic activity) to high frequency (parasympathetic/vagal activity) HRV provides an estimate of autonomic control of the sino-atrial node and has been shown to predict SCD in the dialysis population.

Other tests to assess autonomic dysfunction (baroreceptor reflex, heart rate turbulence) and myocardial impulse conduction (signal averaged ECG) have been attempted in small studies of dialysis patients. Unfortunately, outcome data does not convincingly demonstrate a discriminatory role for these tests in ESRD patients.

1.3.5 Prevention of sudden cardiac death in ESRD patients

Primary and secondary prevention of SCD had been extensively investigated in high risk groups such as post MI and heart failure patients. However, data are absent for ESRD patients due to their exclusion from interventional studies and absence of post hoc sub group analyses. Nonetheless, some interventions have been evaluated.

1.3.5a β adrenergic blockers

The use of β blockers to prevent SCD has been established by many interventional trials for high risk cohorts (post MI, congestive cardiac failure). In a large retrospective study from the USRDS, β blocker therapy was associated with reduced all cause mortality in haemodialysis patients followed for 7 years (119). Cice et al demonstrated reduced CV deaths (68% reduction over 24 months) in haemodialysis patients with dilated cardiomyopathy (n=114) randomised to receive carvedilol instead of placebo (120). In this study there was a trend towards reduced rates of SCD, but this did not reach statistical significance. In a further study of

haemodialysis patients who had survived cardiac arrest (n=729), β blocker therapy was significantly associated with improved survival after 6 months and the effect was greater at higher doses of treatment (121).

1.3.5b ACE inhibitors/Angiotensin II receptor blockers

ACE inhibitors and ARBs have been shown to reduce mortality in patients with significant myocardial diseases and normal renal function (122). Unfortunately, there have been few adequately powered, randomised trials in ESRD patients, and thus a significant effect in reducing sudden death has not been convincingly demonstrated. In dialysis patients, use of ACE inhibitors has not been significantly associated with improved survival of ESRD in the absence of heart failure.

- In a randomised control trial of fosinopril in ESRD patients with normal LV function on echocardiography (n=397), there was no significant difference in rates of CV events between treatment and placebo groups, although there was a trend towards lower CV events in the fosinopril treated arm (123).

AIIRBs have been shown in two prospective trials to improve CV prognosis in ESRD patients. However numbers of patients recruited were small:

- Takahashi et al showed in 80 haemodialysis, that treatment with candersartan significantly reduced CV events compared to placebo (7/43 candersartan vs. 17/37 placebo; $p<0.01$) (124).
- In a larger prospective study (n=366), Suzuki et al demonstrated treatment with ARB reduced fatal and nonfatal CV events (HR 0.51), when adjusted for sex, age,

presence of diabetes, and systolic blood pressure compared to placebo treated patients. There was a lower mortality rate in the treatment group compared to placebo, however this did not achieve statistical significance (125).

For ACE inhibitors and ARBs, larger prospective studies are needed to establish their role in reducing SCD in ESRD patients.

1.3.5c Statins

As mentioned in section 1.2.2b, statin therapy in patients with no renal disease has been shown to be effective in preventing CV events including sudden cardiac death (126). However, as demonstrated by the 4D and AURORA studies (24; 25), although therapy with statins significantly reduces total and LDL-cholesterol serum concentrations, it does not significantly reduce SCD rates in haemodialysis patients, highlighting the differing mechanisms of SCD between uraemic and other cardiomyopathies.

1.3.6d Implantable defibrillators

No prospective trials have demonstrated benefit of ICD insertion in ESRD patients for primary prevention of SCD. These patients were excluded from original ICD trials or sub group analyses have not been published. In addition, it is not clear whether criteria used in the non renal populations to identify high risk groups (e.g. low ejection fraction) are relevant to ESRD patients.

In contrast to results from observational in heart failure populations, it has been difficult to demonstrate a statistically significant benefit of ICD insertion in ESRD patients due to co-morbid conditions:

- In a study of 585 ICD recipients, 19 were previously receiving haemodialysis and although dialysis was a significant predictor of VTA or ICD discharge (HR 2.30), median survival was significantly lower in the dialysis patients compared to the non-dialysis cohort. The authors concluded that other co-morbidities contributed to reduced survival in the dialysis cohort (127).
- In retrospective analyses from the USRDS of ESRD patients that survived a VTA, ICD insertion was shown to improve survival. Although rates of insertion were low in patients where ICD was indicated according to AHA/ACC guidelines (8%), ICD implantation was significantly associated with reduced mortality (HR 0.58) when adjusted for other co-morbid conditions (128).
- In a smaller, single centre study (n=78) comparing stage 3 CKD to dialysis patients, ICD insertion was significantly associated with improved survival in the non dialysis population. There was no survival benefit conferred by ICD insertion in the dialysis cohort (n=45) (129).

Although, life table estimates for survival probability after ICD insertion published by the USRDS have demonstrated a theoretical benefit for primary and secondary prevention of death, sufficient prospective data are lacking. The AHA/ACC guidelines do not exclude ESRD patients from ICD insertion for primary prevention of SCD. Nonetheless, only 15% of ICDs inserted in ESRD patients were for primary

prevention between 1996 and 2003 suggesting underutilisation in patients in whom ICD would be indicated (128).

Overall, there is a reluctance of cardiologists to insert these devices because of a lack of prospective data and high complication rates (bleeding, infection) in ESRD patients (130). ICD insertions may have a role in primary and secondary prevention of SCD in ESRD patients and appropriate prospective studies (e.g. ICD2 study) are currently underway. In addition, appropriate selection of patients based on LV function +/- EP characteristics may be needed to demonstrate a significant effect of ICD insertion on patient survival.

1.4 Assessment of uraemic cardiomyopathy

In this section clinical methods of assessing abnormalities of uraemic cardiomyopathy will be discussed.

1.4.1 Echocardiography

Echocardiography remains the most convenient, inexpensive and best tolerated imaging method to assess myocardial function. It uses ultrasound at wave frequencies between 2-20 MHz to penetrate through non-homogenous tissue. These waves are reflected at different acoustic impedance which are recorded and displayed as monochromic dots. The position of dots is determined by location of the reflecting tissue and intensity of image dependent on acoustic impedance. Ultrasound energy is generated by a transducer that not only emits but detects reflected waves to produce an image.

Since its introduction in 1954, most studies employ M- mode echocardiography since it is the easiest form of image to produce and analyse. M-mode echocardiography involves the use of a single beam of ultrasound to produce a one dimensional image of the moving heart along the plane of interest. Scrolling images over the time period of acquisition are generated, and thus allows measurements of cardiac dimensions and detailed information of motion patterns depending on transducer angulation. Time relationship analyses are also performed when ECGs and heart sounds are collected at image acquisition. Although resolution of images in M-mode echocardiography is good, it does not allow structural visualisation of the heart or spatial relationships of the structures during the cardiac cycle. Two dimensional echocardiography (2DE) scans are obtained from the transducer in 2 perpendicular planes to give detailed information on cardiac anatomy including LV geometry.

In both the clinical setting and research studies, M-mode images are still used to calculate LV mass (usually reported as LV mass index which is corrected for body surface area and recorded as g/m^2). Measurements of posterior wall, internal LV dimensions at end diastole, and interventricular septal thickness are recorded and conventional "cube" calculations (see Formula 1 below) performed to estimate LV mass (131). These calculations have been validated in normal shaped hearts from human autopsies, however are not as accurate in distorted ventricles (such as specific cardiomyopathies) (132). In this situation, it has been recommended that more complex calculations using 2DE images be utilised.

Formula 1 Example of "cube" calculation for estimating LV mass from M mode measurements (131)

Penn Formulae LV mass = 1.04 ([LVIDD + PWTD + IVSTD] ^{3}- [LVIDD] ^{3}) -13.6 g

LVIDD= LV internal diameter diastole,
PWTD= posterior wall thickness diastole
IVSTD= interventricular septum thickness diastole

LV function can be estimated from M-mode LV end diastolic and end systolic internal diameters to calculate LV ejection fraction. Previously used parameters such as fractional shortening have been discarded since this overestimates contractility in patients with abnormal myocardial due to differential transmural contractility. Two-dimensional echocardiography also allows accurate estimation of LV function using the biplane method of disc (Simpson's rule) to calculate end systolic and diastolic volumes after tracing of LV epi- and endocardial borders from 2 and 4-chamber views. Furthermore, left atrial volume (LAV) can reliably be determined using similar techniques from 2DE and has been validated in coronary angiography and contrast enhanced CT studies (133). This will be discussed in more detail in Chapters 2 and 5.

Original studies demonstrating significant cardiac structural changes in patients with CKD and ESRD used echocardiography. These abnormalities included detection of uraemic pericardial effusions, valvular calcification and ventricular wall thickening. As mentioned before, studies from Newfoundland, Canada by Parfrey and Foley published in the 1980s and 90s were the first to demonstrate a convincing association with echocardiographic abnormalities and poor outcome in dialysis patients (47;134).

However echocardiographic assessment of LV mass depends on LV internal dimensions, which in turn depend on cardiac preload. In dialysis patients there are great variations in volume status during the inter-dialytic period resulting in significant changes in LV chamber dimensions. Furthermore, due to the cubed calculations used to estimate LV mass, any potential errors may be magnified (Formula 1). As stated above, calculations based on M-mode measurements have been validated in healthy hearts. Geometric assumptions of these calculations (such as cubic shaped LVs) make LV mass estimation inaccurate in patients with LVH and thus do not apply to ESRD patients who often have features of uraemic cardiomyopathy (132;135). The inaccuracies of echocardiography to assess LV mass in ESRD patients will be discussed below.

Newer techniques to assess LV mass in distorted ventricles are currently being assessed including 3D echocardiography (usually real time) which requires no geometric assumption to assess LV size and has been shown to have reduced inter-observer variation and improved reproducibility (136). There have been few studies using this technique in patients with CKD or ESRD.

1.4.2 Cardiovascular magnetic resonance imaging

Cardiovascular MRI (CMR) is the "gold standard" method for measuring cardiac dimensions and function. Due to rapid development in hardware and software, CMR has been established as a reliable and clinically relevant imaging modality in cardiology.

1.4.2a Principles of magnetic resonance imaging

MRI is based on the principle of nuclear magnetic resonance. Protons and neutrons spin on their own axis within atomic nuclei. When a nucleus has an odd mass number, the nucleus is left with a net spin and as a result of the (positive) charge and spin, develops a magnet field (the direction and size can be represented by a magnetic moment). The human body has very high water content. When protons (hydrogen nuclei derived from water) are placed in an external magnetic field, their magnetic moments align themselves (either parallel or anti-parallel) in line with the direction of the external magnet. The net magnetisation vector (NMV) is dependent on which directions of magnetic moment are in excess within the field. Each nuclei begins to precess (or wobble) on its own axis and the speed of rotation is dependent on the size of the external magnetic field.

When a radiofrequency (RF) pulse is applied at the same frequency of the specific precessional frequency of the hydrogen nuclei and at 90° to the external magnetic field, the nuclei begin to resonate (absorb energy from the RF) which causes the NMV to rotate to a position towards the plane of the external RF. Other nuclei are not affected because they require RFs pulses of a different frequency to cause their nuclei to resonate. Once the RF pulse stops, the NMV recovers to its former position releasing an MR signal that is recorded by a receiver coil. Image acquisition, contrast, and signal intensity are dependent on the relaxation of the NMV producing T1 (longitudinal) recovery and T2 (transverse) decay at the same time and the density of protons in the tissue. In broad terms, the properties of air, fat and fluid allow for sufficient image contrast to provide high resolution images.

Images are obtained using pulsed sequences which consists of a series of RF pulses applied at different duration, strength and intervening time periods with external magnetic field gradients adjusted for the tissue of interest. In CMR, spin-echo and gradient-echo pulsed sequences are used and image acquisition is gated to the patient's ECG at different stages of the cardiac cycle to obtain cinematic (cine) images of the full cardiac cycle. ECG gating can be prospective, where the scans are acquired and triggered by the R wave at the time of scanning or retrospective, where ECG and images are acquired at the same time and digitally reconstructed after data collection. These gating techniques are required to reduce movement artefacts caused by cardiac and respiratory movement. These can also partially be removed by breath holding during image acquisition which usually last 10-15seconds.

1.4.2b CMR and uraemic cardiomyopathy

CMR remains the most accurate, reliable and reproducible method of assessing LV function and chamber size available to cardiologist and radiologists (137). Long and short axis views (Chapter 2) of the LV are obtained, epicardial and endocardial borders are delineated on thin slices of the short axis LV images, and using a Simpson's rule based algorithm, calculation of LV ejection fraction, chamber size and mass are obtained without the need for geometric assumptions. Importantly, these measurements are not dependent on the patient's extracellular/intravascular volume status. In a similar way CMR can reliable assess maximal left atrial volume by measuring LA area and maximal length at end ventricular systole. The CMR protocol is described in detail in Chapter 2.

Cardiovascular magnetic resonance imaging can also reliably detect the presence of myocardial fibrosis using gadolinium for contrast enhanced CMR. Late gadolinium-diethylenetriamine- pentaacetic acid (Gd-DTPA) enhancement (LGE) has been shown to correlate well with endomyocardial biopsy findings of interstial myocardial fibrosis with a sensitivity of 74% and specificity of 81% (138). In ESRD patients, Mark et al demonstrated that presence of LVSD was significantly associated with presence of a subendocardial pattern of LGE on contrast CMR (139). Subendocardial LGE represents areas of previous (commonly silent) myocardial infarction. Based on these results it was postulated that LVSD of uraemic cardiomyopathy is mostly due to atherosclerotic coronary artery disease and its sequelae. Unfortunately, the use of gadolinium based contrast agents in advanced CKD patients has been halted due to the association of their use with development of nephrogenic systemic fibrosis; however newer agents are currently in development. Unfortunately, CMR is not as readily available as echocardiography in many centres due to high cost. In addition, many patients are unable to undergo scanning due to claustrophobia, inability to breathe hold, or presence of ferromagnetic implants (cardiac pacemakers or ICD, intracerebral clips). Given these reasons, the transition from research tool to widely available clinical test has been slow.

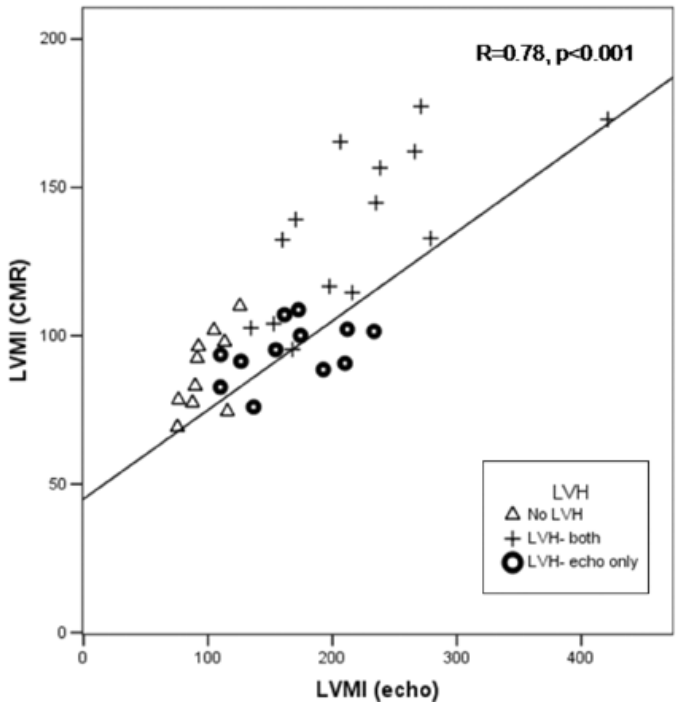
1.4.3 Echocardiography vs. CMR for assessing uraemic cardiomyopathy

As stated above, echocardiography derived measurements of LV function and mass are inherently flawed in ESRD patients and other patient groups who have significant alterations in cardiac shape. M-mode echocardiography, which is the most commonly used means of assessing LV mass, overestimates LVMI compared to CMR:

- In ESRD patients, Stewart et al showed in 35 HD patients assessed within 24 hours of their last HD session, that as LV mass and chamber size increased echocardiographic measurements overestimated mass (Figure 1.4) (135).
- Similar studies performed in hypertensive patients and patients with aortic stenosis and LVH without CKD have also shown that M-mode echocardiography derived measurements of LV mass overestimate LV mass compared to CMR values (132).

In HD patients, pre and post dialysis measurement of LV mass show small changes (up to 10g) on CMR (140). Echocardiogram changes of up to 45g have been recorded and it is likely that, whilst some change may be due to removal of fluid from cardiac interstitial tissues, the large disparities between echocardiography and CMR are due to changes in chamber dimensions during HD and ultrafiltration (141). These changes are amplified due to further cubed computations performed to calculate LV mass.

Figure 1.4 Comparison of LVMI measurement techniques (142)



Greater precision and reproducibility of CMR to detect small, non artefactual changes in LV mass allows studies to recruit much smaller cohorts. For example, Keenan et al have estimated that to detect a 10g drop in LVMI after a therapeutic intervention at a power of 80% and p value of 0.05, the sample size would have to be 505 patients with 2D echo and only 14 using CMR,(137). Although these theoretical power calculations provide significantly exaggerated results, they adequately highlight the benefit that CMR would provide over echocardiography.

1.5 Cardiac magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) uses the spin property of nuclei to allow non-invasive assessment of the biochemical composition and metabolic activity of tissues of interest without the need of external contrast media/tracers. MRS provides this information for nuclei that contain atoms with nuclear spin. As stated before, the nuclear spin of atoms with odd mass numbers results in development of magnetic fields/moment and thus susceptibility to nuclei specific (dependent on the gyromagnetic frequency of the nucleus) radiofrequency waves to cause wobble of these nuclei on their axis. In cardiac MRS, ^{31}P is the most extensively studied nucleus. Other nuclei of interest include ^{1}H, ^{13}C and ^{23}Na.

MRS has been used experimentally for over 30 years, however its use in clinical practice has been limited due to the very low concentration of nuclei and subsequent low resolution of metabolic/biochemical images acquired. Nonetheless, ^{31}P MRS of the human heart has been obtained to study cardiac high energy phosphate (HEP) metabolism.

1.5.1 Principles of ^{31}P MRS

Hydrolysis of adenosine triphosphate (ATP) provides free energy for energy consuming reactions in cells:

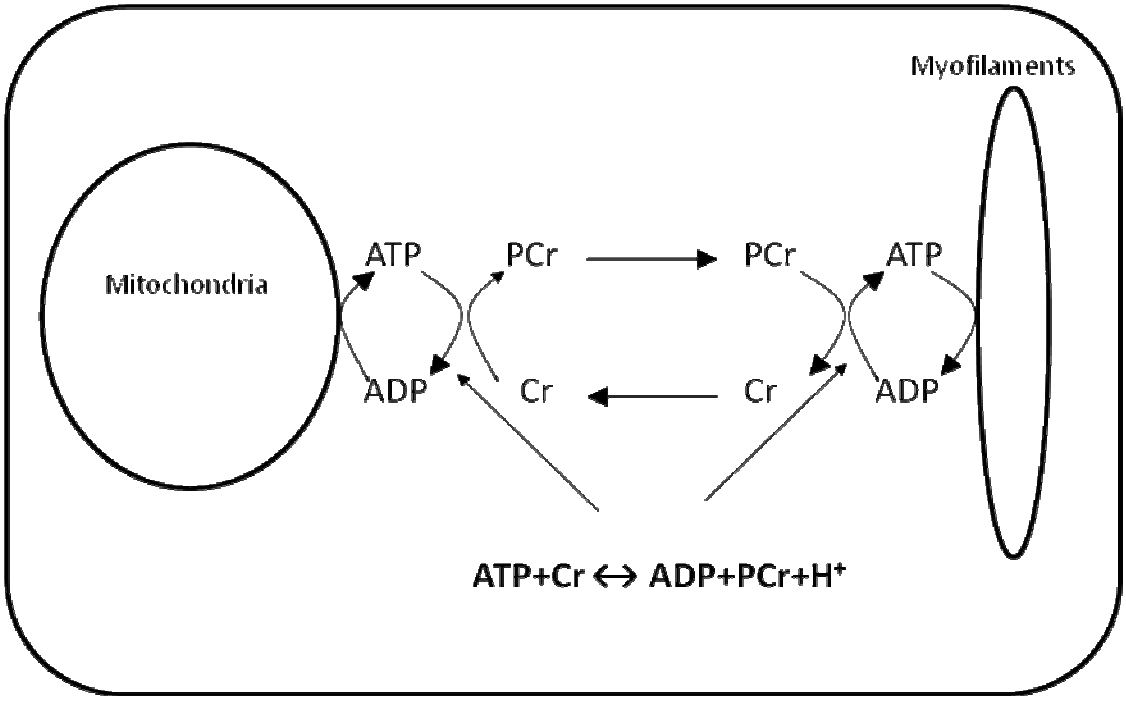
$$ATP \leftrightarrow ADP + Pi$$

ADP= adenosine diphosphate

Pi= inorganic phosphate.

Phosphocreatine (PCr) is a high energy phosphate compound which acts as an energy transfer molecule in the “creatine kinase (CK)/PCr energy shuttle” (see Figure 1.5). The high energy phosphate bond is transferred from areas of ATP production (mitochondria) to the myofilaments or other sites of ATP utilisation by PCr where the back reaction is performed. Newly formed ATP is then used for cardiomyocyte contraction.

Figure 1.5 Schematic representation of creatine kinase (CK)/PCr energy shuttle.



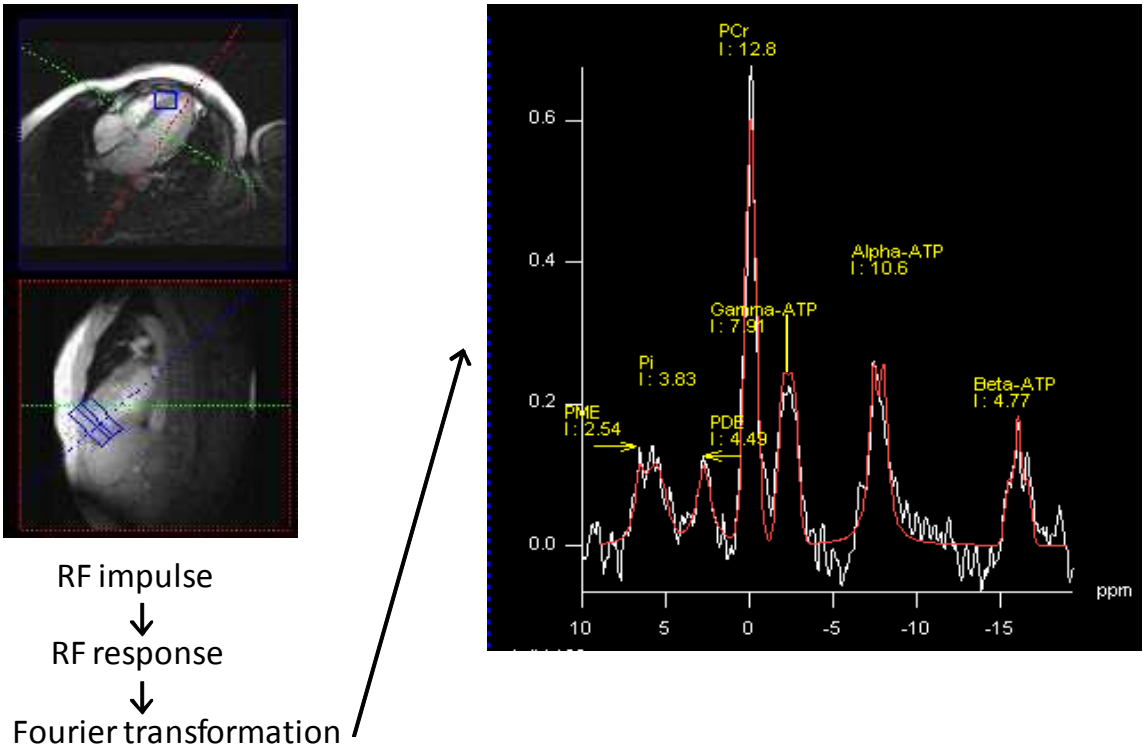
This shuttle is required because free intra- cytoplasmic ADP concentrations are too low to allow adequate diffusion into mitochondria for ATP production. Elevated free ADP also inhibits intracellular enzyme function, thus when [PCr] is normal the shuttle strives to keep [ADP] to as low as possible since the chemical equilibrium favours ATP production. [ADP] will rise only when [PCr] are depleted. During myocardial activity when [ATP] is low, the equilibrium shifts to ATP synthesis. Thus PCr acts as a buffer to resist changes of intracellular ATP concentration (143). ^{31}P-MRS allows examination of relative concentrations of PCr, ATP and inorganic phosphate (Pi).

1.5.2 Methodology of ^{31}P MRS

MR scanners that allow spectra acquisition use the same magnets used for conventional CMR imaging (usually 1.5T or 3T), however nucleus specific coils and software to process specific sequences are needed. Prior to spectra collection, the magnetic field must be homogenised as much as possible using shim coils. Furthermore, to account for cardiac movement during scanning, scans are performed with cardiac gating. ^{1}H images are obtained of the myocardium to allow localisation of specific voxels over areas of interest (Figure 1.6).

After a ^{31}P specific radiofrequency pulse causes spin excitation, the resulting MR signal (free induction decay) is recorded. Subsequent fast Fourier transformation splits the time varying decaying MR signal into it frequency components generating an MR spectrum. Small differences in the MR signal for different ^{31}P containing molecules are caused by shielding of the nuclei of interest by surrounding nuclei (hydrogen, carbon) -so called "chemical shift". The area under each resonance peak in the spectrum is directly proportional to the concentration of each ^{31}P containing molecule in the area of interest allowing measurement of relative concentrations. (Figure 1.6) Absolute concentrations are much more difficult to obtain and involve calibration against a ^{31}P containing molecule of known concentration at the time of scanning. More information regarding acquisition of ^{31}P-MRS is provided in section 2.5.

Figure 1.6 Acquisition on ^{31}P spectra in a healthy volunteer



A typical ^{31}P spectrum is shown in Figure 1.6 depicting the resonances of interest: three ^{31}P atoms of ATP (α, β and γ), phosphocreatine (PCr), inorganic phosphate (Pi) and phosphodiesters (PDE)/ membrane phospholipids (PME). Although not shown due to its proximity to the Pi resonance, 2, 3-diphosphoglycerate (2,3-DPG) resonances can be detected due to the presence of red blood cells in the voxel of interest.

The most common way of quantifying ^{31}P spectra from the human heart is by calculating PCr: ATP ratios which are considered a measure of the cardiac energetic state. The CK/PCr chemical equilibrium favours ATP over PCr synthesis by a factor of almost 100. Thus ATP concentrations will only decrease when PCr concentration is substantially depleted i.e. the buffer is exhausted. However, PCr: ATP ratio is

limited since it may underestimate changes in PCr if ATP levels are reduced and does not provide information of changes in relative ATP concentrations. A further limitation of ^{31}P MRS is that the entire heart cannot be investigated due to limitation in acquisition voxel size. Most studies in patients with homogenous myocardial changes (eg valve disease, dilated cardiomyopathy) have investigated the LV antero-apical wall (144;145). Another measurement which has been evaluated is phosphodiester/ATP ratio which is believed to measure cell membrane integrity in animal models; however its use in clinical studies is limited.

1.5.3 Clinical studies on ^{31}P-MRS

In healthy volunteers, PCr:ATP ratios have been measured with values of 1.0-2.6 (mean 1.8) and this wide range is most likely due to differing spectra acquisition systems and analyses software. Nonetheless, PCR: ATP levels have a reciprocal relationship with age and have been demonstrated to fall in healthy individuals after atropine-dobutamine stress to 85% maximal heart rate (146).

Patients with stable symptomatic heart failure, reduced LVEF, and valvular heart disease have been shown to have reduced PCr: ATP ratios (145). Furthermore, in patients with dilated cardiomyopathy, PCr: ATP ratio <1.6 has been significantly associated with poorer survival (144). Heart failure is associated with impaired energy metabolism due to alteration in substrate consumption (fatty acid, carbohydrate), impaired oxidative phosphorylation, and reduced HEP metabolism (147). Furthermore, treatments with β blockers and ACE inhibitors/ARBs have been associated with elevation of PCr: ATP ratios and symptomatic improvement in

patients with dilated cardiomyopathy, suggesting that improved cardiac HEP metabolism may provide one of the pharmacological benefits of these drugs.

As one would expect, patients with current or past history of coronary artery disease have reduced resting and stress PCr:ATP ratios in areas of myocardial scarring or regional wall motion abnormalities. Similarly, in symptomatic women with normal coronary arteries and echocardiograms exercise PCr:ATP ratios are reduced compared to resting levels and presumed a consequence of microvascular ischaemia (148).

Athletes with physiological LV hypertrophy do not have reduced PCr: ATP ratios. However, studies in patients with hypertension related LVH have demonstrated reduced PCr: ATP ratios at rest and during exercise. Patients with type 1 and 2 diabetes mellitus and normal LVEF have reduced PCr: ATP ratios suggesting that altered cardiac phosphate metabolism (presumably due to small vessel myocardial ischaemia and handling of free fatty acids) may partially account for higher levels of heart failure within this population(143).

Two observational studies has investigated resting PCr: ATP levels in patients with kidney disease.

- In type 1 diabetic uraemic patients. Perseghin et al (149) studied 43 patients (11 diabetic uraemic patients, 5 non diabetic uraemic patients, 11 diabetic kidney transplant recipients, and 16 diabetic kidney pancreas recipients) and 24 non diabetic controls (11 non diabetic kidney transplant recipients and 13 healthy controls).

Patients with uraemia (diabetic and non diabetic) had reduced PCr: ATP ratios compared to healthy controls and kidney transplant recipients. Diabetic uraemic patients had the lowest PCr: ATP ratios leading the authors to conclude that altered myocardial HEP metabolism may contribute to accelerated LV dysfunction in diabetic uraemic patients. The authors also suggested that impaired HEP metabolism may be partially reversed by successful transplantation.

- A small study in haemodialysis patients (n=14) demonstrated a significant reduction in PCr: ATP in haemodialysis patients compared to control patients with (n=7) and without LVH (n=7). In this study no association was found between PCr:ATP and features of uraemic cardiomyopathy (150).

The clinical use of MRS has been limited due to the availability of CMR and noisy signals obtained at lower magnetic field strengths (<1.5T). As stronger MR systems become readily available to clinicians and better resolutions of spectra acquisition are achieved, MRS may develop into a useful tool to evaluate biochemical/metabolic function in addition to myocardial abnormalities detected by CMR.

1.6 Aims of this thesis

The aims of this thesis are to:

- Identify the determinants of LV abnormalities, measured by CMR, in haemodialysis patients from clinical, dialysis and blood characteristics.
- Assess the effect of these CMR detected LV abnormalities on all cause and CV survival.
- Establish the effect of left atrial volume, measured by CMR, on survival in ESRD patients with LVH.
- Estimate the prevalence of abnormal MTWA in a cohort of ESRD patients and identify associations with features of uraemic cardiomyopathy.
- Establish the effect of LV abnormalities on high energy phosphate metabolism measured by ^{31}Phosphorus MR spectroscopy in ESRD patients..
- Determine whether renal transplantation has an effect on LV mass measured by CMR.

1.6.1 Hypotheses

These studies are designed to test the hypothesis that uraemic cardiomyopathy is associated with specific electrophysiological, biochemical, and other cardiac abnormalities which may have an influence on the outcome of ESRD patients.

1.7 Outline of this thesis

Data from six studies are presented in chapters 3 to 8 of this thesis. These studies investigate prognostic and pathophysiological features of uraemic cardiomyopathy:

Chapter 3 : A study of independent predictors of uraemic cardiomyopathy in haemodialysis patients

Chapter 4 : A study identifying predictors of cardiovascular death in ESRD patients undergoing screening for renal transplantation.

Chapter 5 : A study of determinants of mortality in ESRD patients with LVH: the role of left atrial volume.

Chapter 6 : A study of Microvolt T Wave Alternans in ESRD patients.

Chapter 7 : A study of ^{31}P magnetic resonance spectroscopy in uraemic and hypertensive cardiomyopathy.

Chapter 8 : A study of changes in left ventricular mass after renal transplantation.

Chapter 2

Material and Methods

2.0 Introduction

The major techniques utilised for this thesis provided information regarding myocardial structure and electrophysiology of ESRD patients. Detailed evaluation of cardiac structure was obtained using cardiovascular magnetic resonance imaging (CMR). ^{31}Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) was performed to evaluate myocardial metabolic activity. Cardiac electrophysiology was evaluated using electrocardiography (ECG) and Microvolt T wave alternans measurement during exercise. In this chapter, the background, apparatus, and protocols for these techniques will be described.

2.1 Ethical approval

Ethical approval was obtained from the West Glasgow Ethics Committee for these studies to be performed at the Western Infirmary, Glasgow. All subjects provided written informed consent with forms approved by the Ethics Committee.

2.2 Study subjects

2.2.1 Inclusion criteria

Patients with ESRD were recruited from the renal unit at the Western Infirmary. Patients receiving regular haemodialysis and peritoneal dialysis were assessed. Haemodialysis patients were studied on a non-dialysis day. Since the risk of cardiovascular death is similar between those patients who receive and those near to requiring renal replacement therapy, patients who would require renal replacement therapy within 6 months were also assessed. According to K/DOQI classification (151), these patients would be classified as chronic kidney disease stage 5 (CKD 5).

Eligible patients were identified by the renal transplant assessment team for cardiovascular screening as part of their preparation for inclusion on the renal transplant waiting list. Death in renal transplant recipients is most commonly a result of cardiovascular disease. In keeping with Renal Association guidelines (42), pre- transplant cardiac assessment is necessary to ensure recipient survival is not compromised immediately after transplantation. Furthermore, screening is recommended to reduce peri- and post operative cardiac complications. Factors prompting referral for cardiac assessment in our centre are:

- Age≥ 50 years of age
- Presence of diabetes mellitus
- Prior history of ischaemic heart, cerebrovascular or peripheral vascular disease
- Family history of cardiovascular disease in a first degree relative
- Previous abnormal ECG or cardiac stress test indicating ischaemic heart disease
- Previous evidence of left ventricular (LV) abnormalities on echocardiography
- The clinical opinion of the transplant assessment team (which includes a consultant transplant surgeon and nephrologist)

The assessment included clinical history, examination, standard 12-lead ECG, Standard Bruce Protocol exercise test, assessment of LV structure and function by CMR and blood sampling. Clinical history of ischaemic heart disease was defined as past or current history of angina pectoris, myocardial ischemia/infarction and/or coronary revascularisation procedure. After review of these results by an independent cardiologist, myocardial perfusion and/or coronary angiography scanning were performed. The decision regarding addition onto the renal transplant

waiting list was made at a separate, independent clinic involving a transplant surgeon and physician. The results of non invasive (and invasive, if performed) cardiovascular assessment tests were available to the assessing surgeon and nephrologists before a final decision was reached. However, no specific recommendation was provided regarding the suitability of an individual patient for renal transplantation based on cardiovascular assessment results.

2.2.2 Exclusion criteria

Patients were excluded from these studies if magnetic resonance imaging was contraindicated (presence of ferromagnetic implants or permanent cardiac pacemaker, claustrophobia and pregnancy). Patients were also excluded from MTWA testing if their underlying cardiac rhythm was atrial fibrillation as this precludes testing using HearTwave II system (Cambridge Heart, Bedford, Mass.) (152).

2.3 Cardiovascular magnetic resonance scanning

Patients underwent CMR scanning using a 1.5 Tesla MRI scanner (Sonata, Siemens, Erlangan, Germany). As stated before, this technique provides a detailed, reliable, reproducible and volume independent measurement of cardiac structure and is considered the most accurate method for assessing ventricular dimensions in patients. Scans were performed and analysed by myself or a trained CMR radiographer (Tracey Steedman, Glasgow Clinical Research Initiative, Western Infirmary, Glasgow).

2.3.1 Timing of CMR scan

To reduce the effect of interdialytic fluid accumulation on ventricular wall thickness, haemodialysis patients underwent scanning the day after a dialysis session. Peritoneal dialysis patients were scanned at their "dry weight" according to their dialysis clinical records.

2.3.2 CMR image acquisition

2.3.2a Patient position

Patients were placed head first into the scanner in the supine position. A handheld alarm provided patients with the means of contacting the investigator. Headphones were also used to provide noise protection and convey breathing instructions. An anterior chest 6 channel phase array coil was used to acquire images.

2.3.2b Assessment of left ventricular mass, chamber size and function

An ECG gated fast imaging with steady-state precession (true FISP) sequence during end expiratory breath holding was used to acquire cine images in long axis planes (vertical long axis, horizontal long axis, left ventricular outflow tract) followed by sequential short axis LV cine loops (8 mm slice thickness, 2 mm gap between slices) from the atrioventricular ring to the apex. The formal protocol was (Figures 2.1-2.4):

1. An initial multi-slice localiser was performed at end tidal expiration and the optimal transverse section of the LV and inter-ventricular septum was selected (Figure 2.1).

2. A vertical long axis (VLA) localiser of the LV was obtained from the centre of the mitral valve annulus to the apex. From this localiser a subsequent horizontal long axis (HLA) localiser was taken from the mitral valve annulus to the apex (Figure 2.2).
3. Three short axis (SA) localisers were generated from the HLA localiser. Images were obtained at the level of the atrio-ventricular groove parallel to the mitral and tricuspid valve annuli (Figure 2.2).
4. These SA localisers were used to plan cine images. Four and two-chamber, and left ventricular outflow tract (LVOT) cine scans were generated (Figure 2.3).
5. From the 4 chamber scans, a short axis stack was obtained. Two mm scans were obtained at 8 mm intervals from the atrio-ventricular groove to the LV apex.

Imaging parameters, which were standardized for all subjects, included repetition time (TR)/echo time (TE)/flip angle/voxel size/field of view (FoV)=3.14 ms/1.6 ms/60°/2.2 x 1.3 x 8.0 mm/340 mm.

2.4 Analysis of CMR scans

2.4.1 Measurement of left ventricular mass, function and chamber size

Short axis cinema loops of the LV were used to assess LV function (Figures 2.4 and 2.5). LV mass was measured from short axis cine loops using manual tracing of epicardial and endocardial end-systolic and end-diastolic borders. From these images, analysis software (Argus, Siemens, Erlangen, Germany) was used to calculate left ventricular ejection fraction (LVEF) using the equation:

$$\text{LVEF (\%)} = \frac{\text{End Diastolic Volume (ml)} - \text{End Systolic Volume (ml)}}{\text{End Diastolic Volume (ml)}} \times 100$$

Similarly LV mass (LVM), end diastolic volume (EDV) and end systolic volume (ESV) were calculated from these images and indexed according to body surface area (LVMI, EDV/BSA, ESV/BSA respectively). Body surface area was calculated using the Dubois formula (153):

$$\textbf{Body Surface Area} = 0.20247 \times \text{Height (m)}^{0.725} \times \text{Weight (kg)}^{0.425}$$

2.4.2 Values used to define left ventricular abnormalities

LV abnormalities were defined by normal published mean (± 2 standard deviations) LV measurements in healthy volunteers (154). Left ventricular hypertrophy (LVH) was defined as LVMI >84.1 g/m^2 (male) or >76.4 g/m^2 (female). Left ventricular systolic dysfunction (LVSD) was defined as LVEF<55% and LV dilatation was defined as end diastolic volume/body surface area (EDV/BSA)>111.7 ml/m^2 (male) or 99.3 ml/m^2 (female) or end systolic volume /body surface area (ESV/BSA) >92.8 ml/m^2 (male) or 70.3 ml/m^2 (female).

Figure 2.1 Multi slice breath hold localiser in end expiration

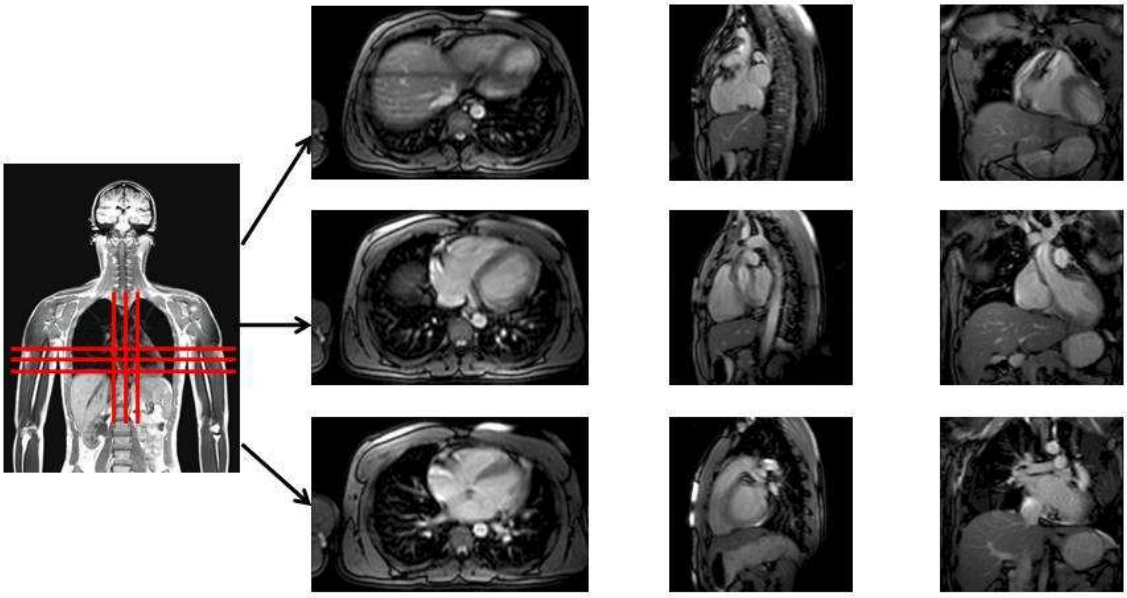


Figure 2.2 Generation of 3 short axis localisers from transverse slice multilocaliser, vertical long axis and horizontal long axis

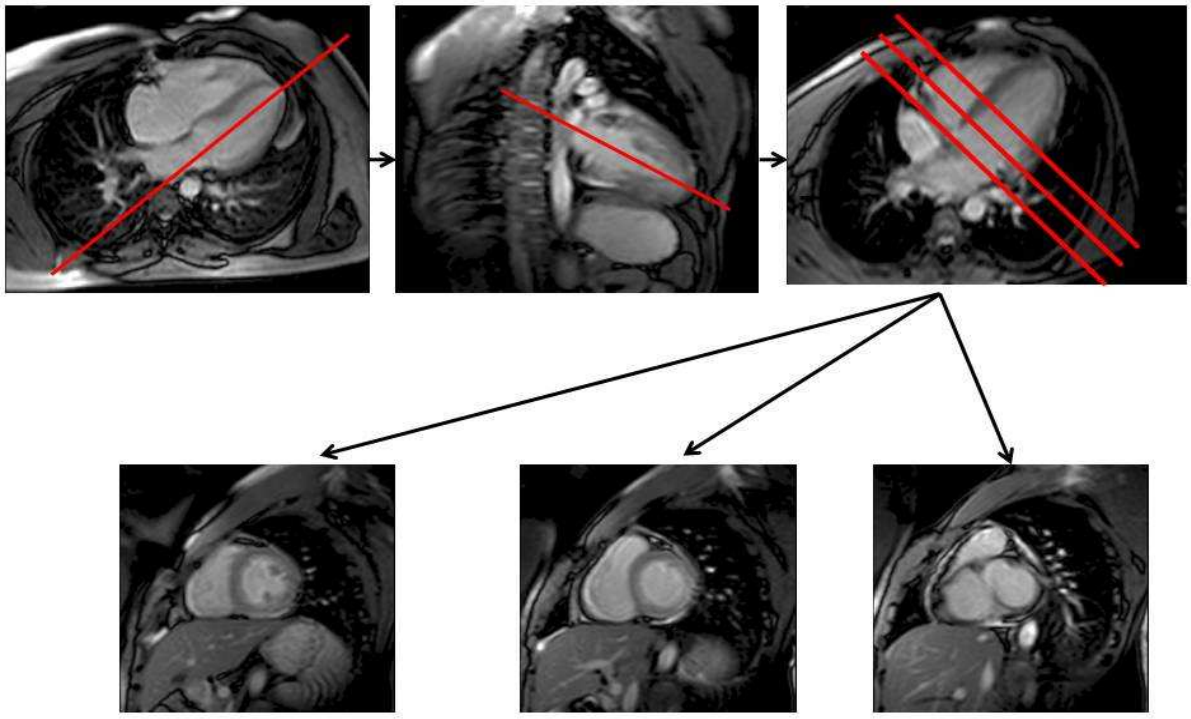


Figure 2.3 Generation of long axis cine images from short axis localiser (arrows correspond to planes highlighted in short axis pilots). Coloured lines (blue, green, red) correspond to plane of image acquisition

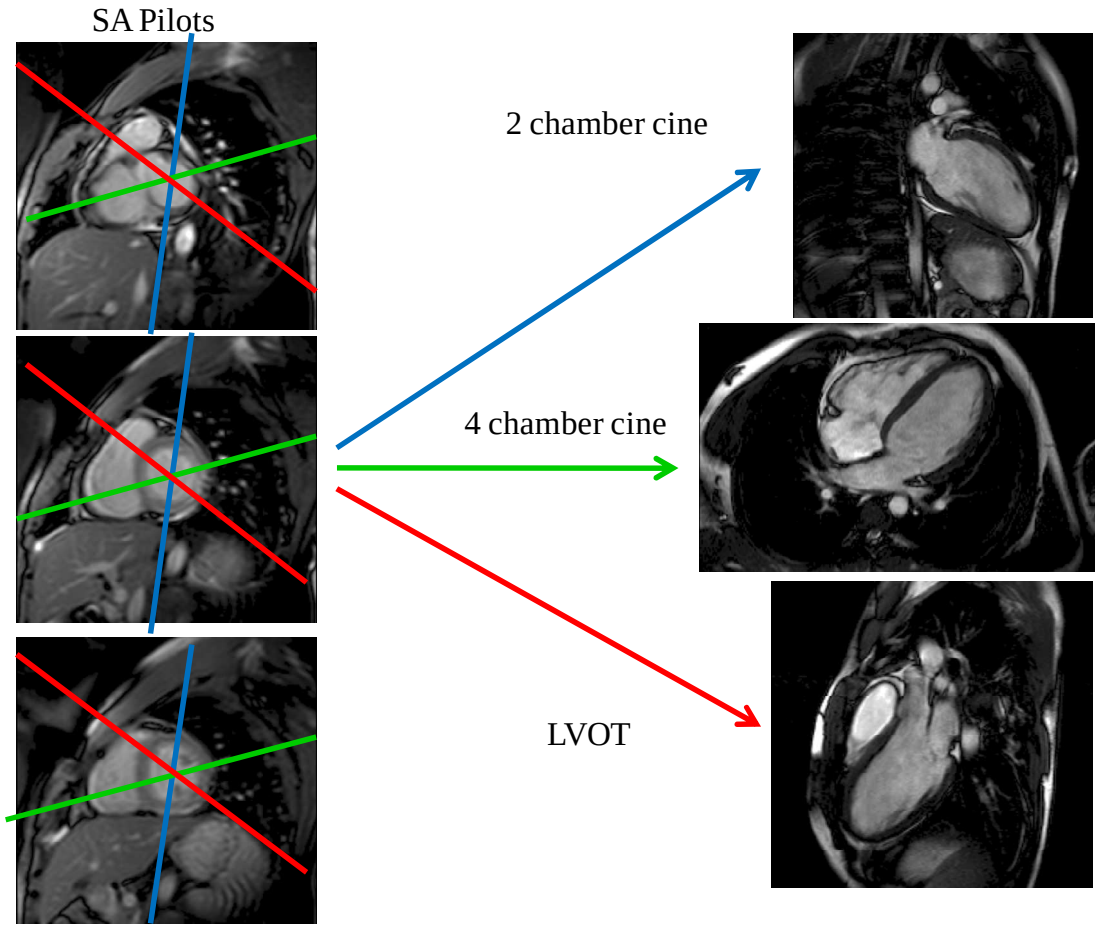


Figure 2.4 Generation of short axis stack images from 4 chamber cine

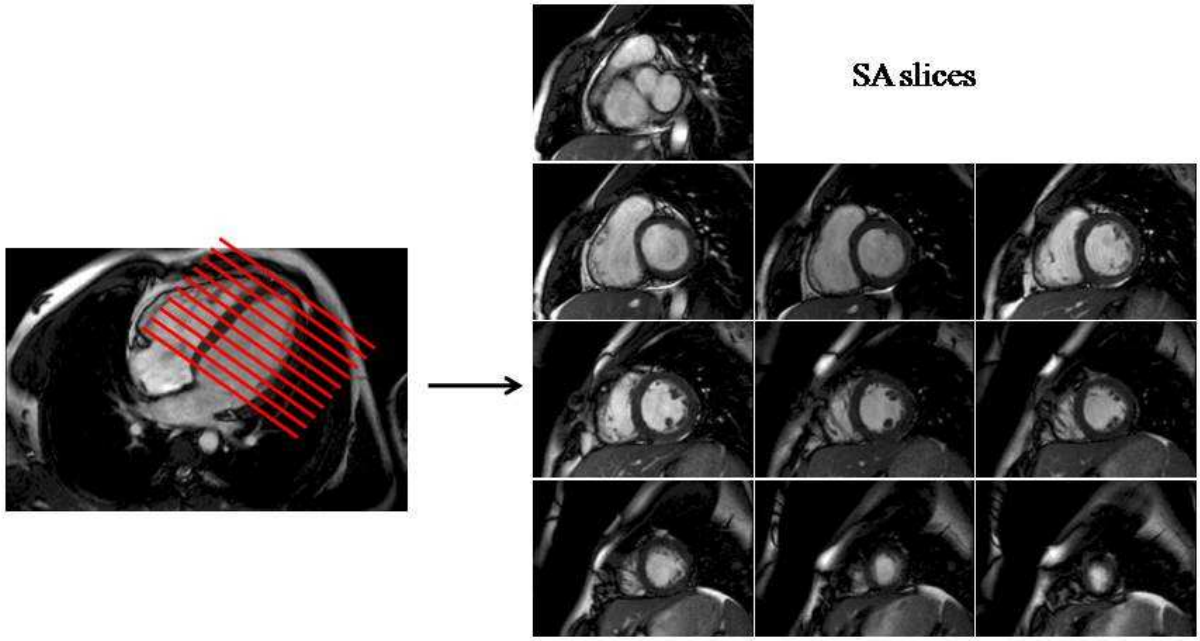
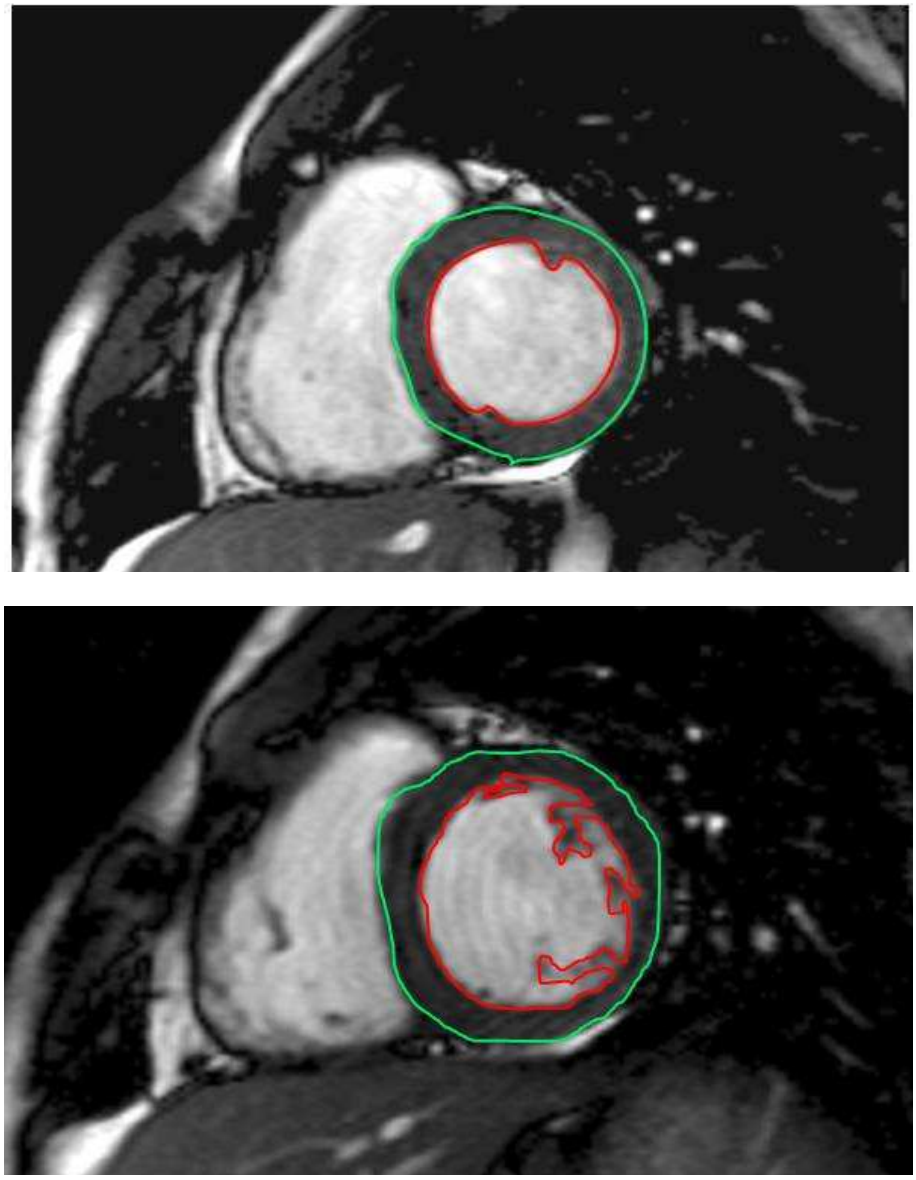


Figure 2.6 Short axis view of left ventricle

(upper panel= basal, lower panel= mid ventricular) with epicardial (green) and endocardial (red) borders traced using image analysis software



2.4.3 Measurement of left atrial volume

The bi-plane area length method for ellipsoid bodies was used (155;156) to measure left atrial volume (LAV). Horizontal and vertical long axis cine images were used to obtain images of the left atrium at maximal filling (Figure 2.7). The atrial lengths and areas were measured from both views using image measurement tools (Siemens, Erlangen, Germany), and LAV calculated using the equation:

$$\textbf{LA Volume (ml)} = \frac{\textbf{0.85 x LA Area}_{\textbf{2 chamber}}\textbf{ (cm}^2\textbf{) x LA Area}_{\textbf{4 chamber}}\textbf{ (cm}^2\textbf{)}}{\textbf{Mean LA Length (cm)}}$$

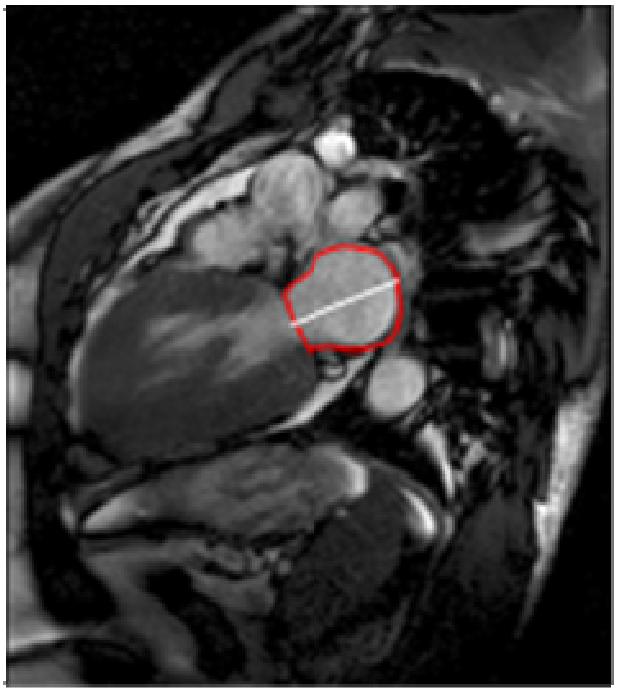
LAV was corrected for body surface area (LAV/BSA). Left atrial appendages were not included in these measurements.

Figure 2.7 Measurement of maximal left atrial volume.

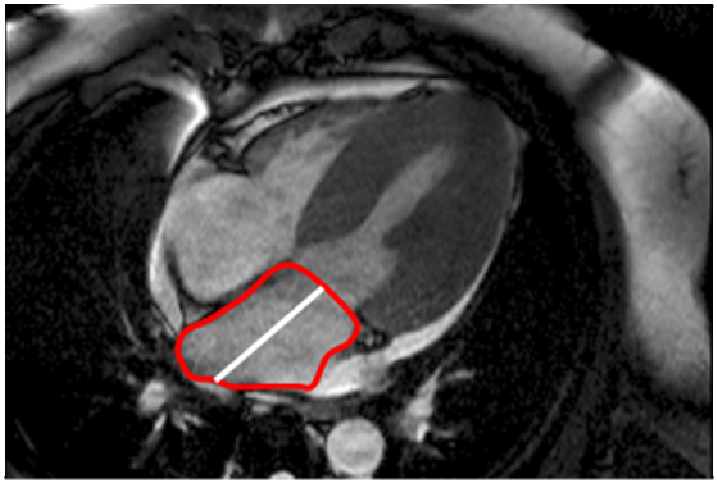
Panel A measurement of LA length (white) and LA area (red) from 2 chamber view.

Panel B, measurement of LA length (white) and LA area (red) from 4 chamber view.

A



B



2.5 ^{31}Phosphorus MR spectroscopy

2.5.1 ^{31}Phosphorus MR spectroscopy acquisition

^{31}Phosphorus MR Spectroscopy (^{31}P-MRS) was performed using a 1.5 Tesla MRI scanner (Sonata, Siemens, Erlangan, Germany). A dedicated spectroscopy surface coil (dual resonant heart/liver ^{31}P/^{1}H coil) was used. As before, patients were placed in the supine position and the coil placed over the left ventricle on the anterior chest wall.

After localisation, pilot scans were performed in the cardiac vertical long axis plane (fast low angle shot (FLASH) images, slice thickness 10mm, TR/TE 7/7.37ms, FoV 350mm), ^{31}P-MRS data were obtained with a 2-D chemical shift imaging sequence (CSI). The acquisition matrix size was 25mm x 25mm and TE = 2.3ms, flip angle =90º, no signal averaging NSA=60. The chemical shift imaging (CSI) grid was positioned over the left ventricle to ensure one voxel covered the LV apex and the remaining voxels provided coverage for the LV superior and inferior walls (Figure 2.7a). Prospective ECG gating was used with an acquisition trigger delay of 100ms and data was acquired during diastole. An optimised radiofrequency pulse (length 2.4ms) centered between γ- and α- adenosine triphosphate (ATP) resonance frequencies was used to ensure uniform excitation of all spectral peaks (Figure 2.7b).

2.5.2 Data acquisition

Spectra were obtained and areas under the curves of interest were measured using spectroscopic fitting software (Siemens, Erlangen, Germany). The spectral resonances for β-ATP, 2,3- DPG and phosphocreatine (PCr) were fitted using prior

knowledge relating to peak frequencies and J- coupling patterns. PCr: β-ATP ratios (PCr: ATP) were calculated accordingly.

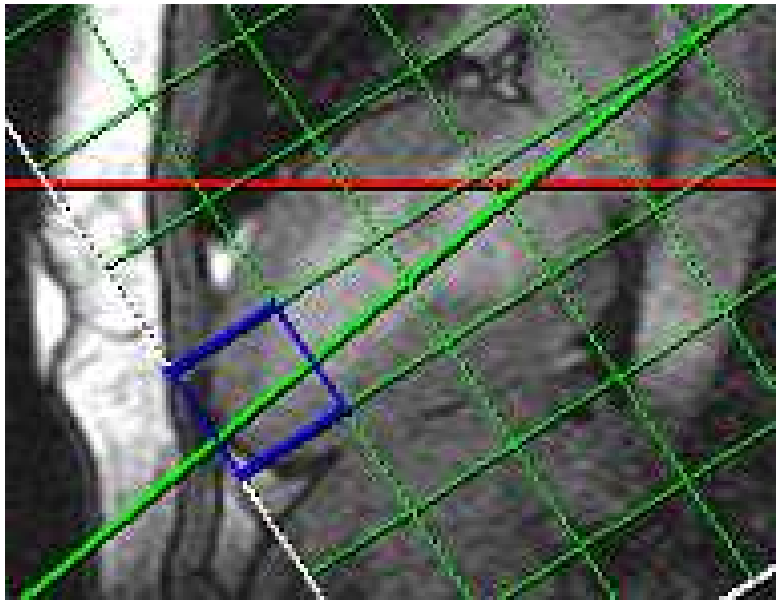
2.5.3 Correction for blood contamination

A correction for intraventricular blood was performed. In addition to causing scatter, intracorpuscular ATP prevents accurate estimation of true myocardial PCr: ATP. Blood contains 2,3 diphosphoglycerate (DPG) which exhibits resonances at roughly 5.4 and 6.3ppm relative to PCr. The effect of blood ATP was corrected using Equation 2.5, which has been validated in patients with dilated cardiomyopathy and healthy volunteers (157).

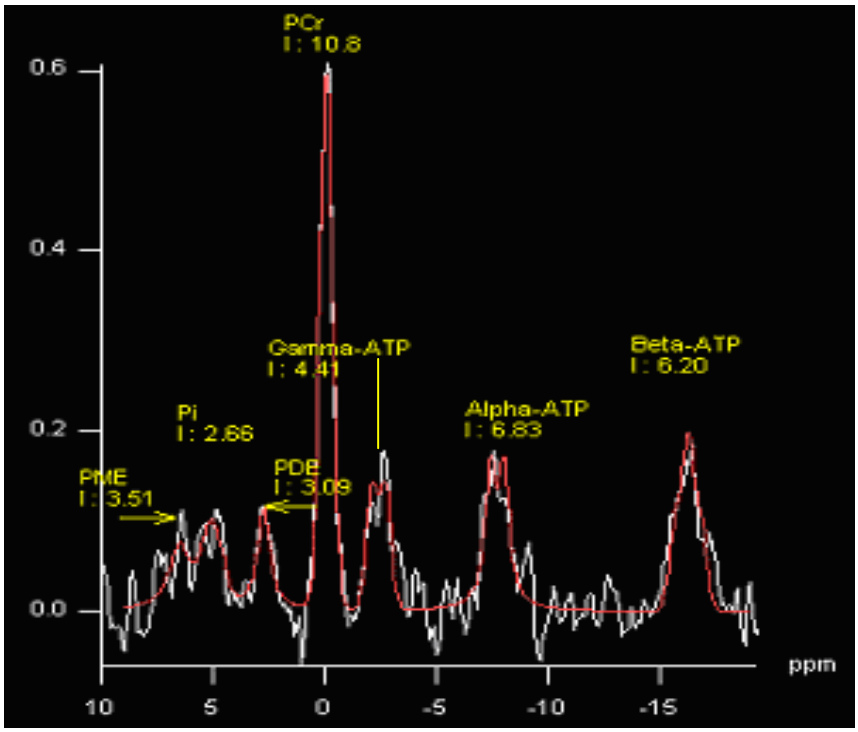
Equation 2.5: $$\beta\text{-ATP}_{\text{Corrected}} = \beta\text{-ATP}_{\text{HEART}} - (0.15 \times 2,3\text{-DPG}_{\text{BLOOD}})$$

Figure 2.7 31Phosphorus MR spectroscopy

(a) CSI grid positioned over the left ventricle superior and inferior walls



(b) Example of ^{31}P MRS obtained from voxel (blue) above



2.6 Microvolt T wave alternans

2.6.1 Exercise testing- microvolt T wave alternans (MTWA)

All tests were performed by the investigator on the day of CMR scanning. Skin was prepared by shaving and cleansing with abrasive electrode gel to ensure close contact with electrodes. Seven standard and seven high resolution electrodes (Microvolt Sensors, Cambridge Heart Inc, Bedford, Mass.) were attached to patients in the standard 12-lead and Frank orthogonal position (158) and connected to a HearTwave II System (Cambridge Heart, Bedford, Mass) for MTWA testing.

An initial check was performed by the device to ensure adequate electrode contact and testing began with acquisition of ECG data at rest for 20 seconds. Patients were then asked to undergo gentle treadmill exercise to allow sufficient elevation in heart rate (HR). Increase in speed and incline was performed to ensure HR elevation to between 100-110bpm for 150 seconds. If patients could tolerate more exercise, a further 90 seconds of walking was performed in order to achieve heart rate between 110 and 120bpm. At the end of the exercise period, patients were allowed to sit at rest until HR was below 90bpm, after which the test was terminated. ECG data was collected digitally by the HearTwave system (108; 159).

2.6.2 Spectral analyses of ECG data

Collected ECG data were interpreted according to standard criteria using spectral analyses and reported using standard automated classification (HearTwave II System, Cambridge Heart, Bedford, Mass). This technique measured amplitude of corresponding points of 128 consecutive T waves where each T wave was measured

precisely at the same time point relative to the QRS complex start. Beat- to- beat amplitude fluctuations were plotted and a fast Fourier transformation was performed to provide quantification of the frequency variation (Figure 2.8). As measurements were taken every beat, the frequencies were in units of cycles per beat. The point on the spectrum corresponding to exactly 0.5 cycles per beat represents the power of T-wave front alternation. Significant alternans was calculated from comparison with the background noise frequency band (0.44 and 0.49 cycles per beat) (160).

After MTWA testing, a positive MTWA result was defined as presence of sustained alternans (sufficient alternans present for at least 1 minute) at heart rates <110bpm on exercise or at rest (even if higher than 110 bpm). A negative MTWA test result was defined as the absence of positive test criteria with a maximum heart rate≥105 beats/min. A test that did not satisfy positive or negative criteria was classified as indeterminate (Figure 2.9). Based on previously published studies (161) results were further classified as "abnormal" (for positive and indeterminate test results) or "negative" (reported as a negative test). If initially an indeterminate result was obtained, immediate retesting was attempted. Reasons for indeterminate test provided by the analysis software were:

- failure to achieve sufficient heart rate rise
- excessive ventricular ectopy during exercise
- a noisy recording due to ECG artefact
- rapid rise through target heart rate of 105-110bpm
- unsustained MTWA (≤1 min)

Figure 2.8 Spectral analyses of ECG and generation of frequency spectrum (162)

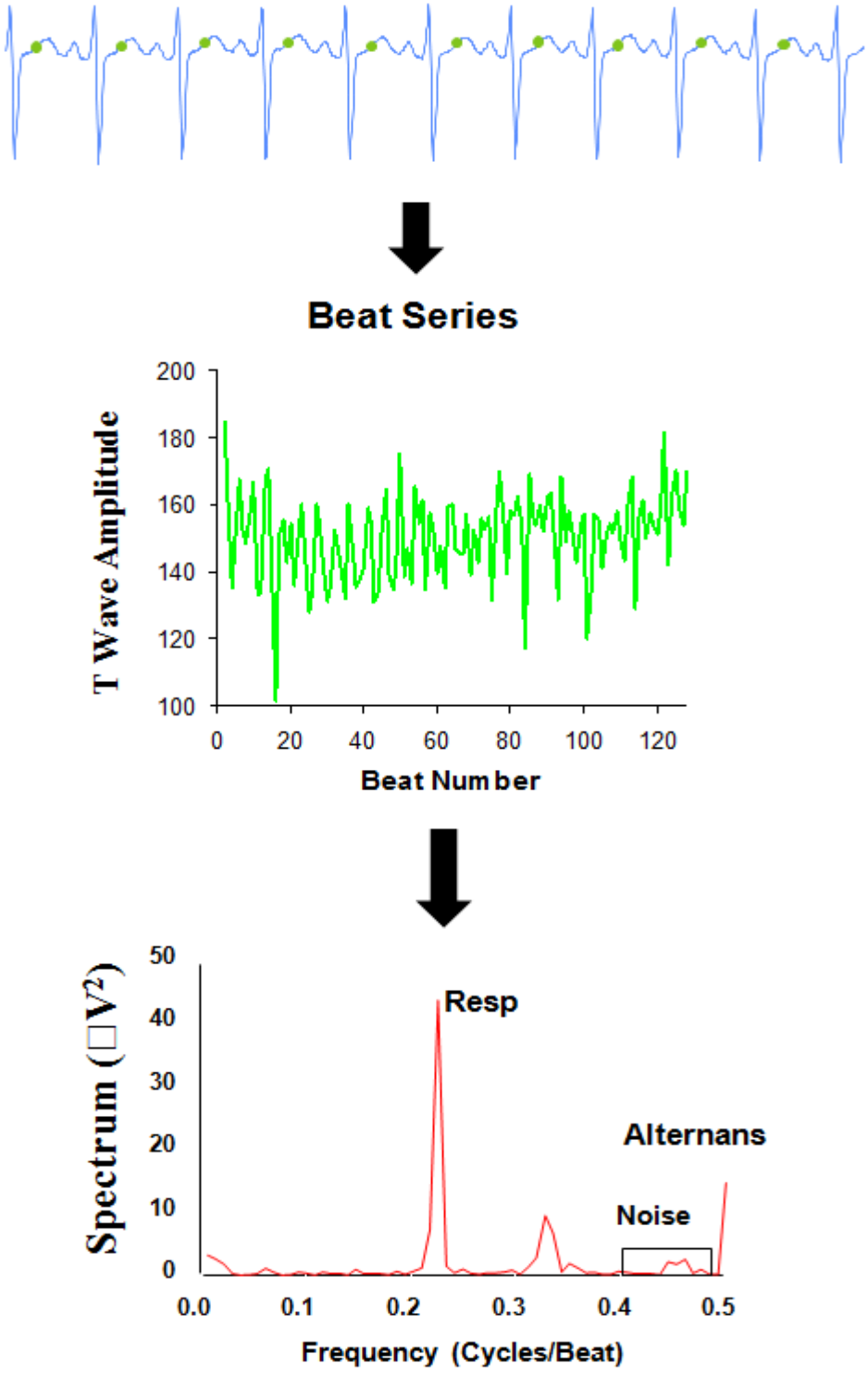
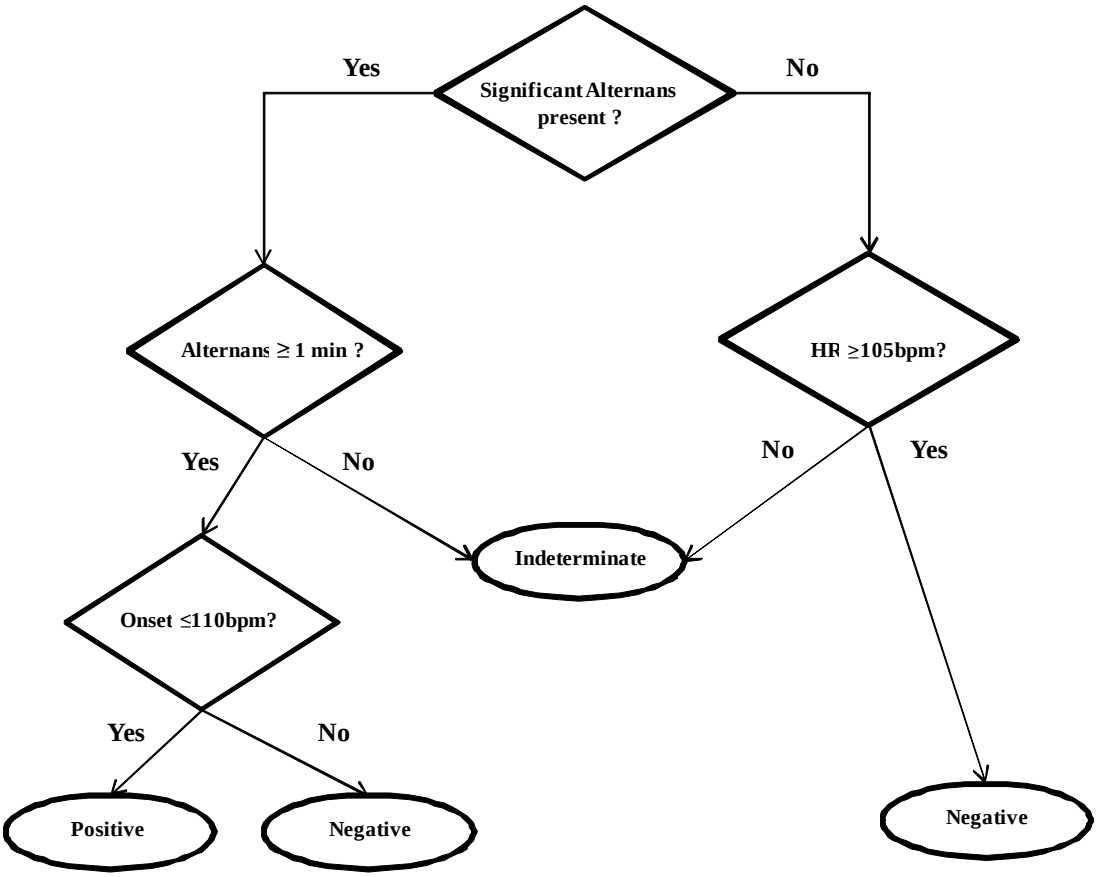


Figure 2.9 Classification of MTWA result based on duration of sufficient alternans and heart rate achieved during exercise.

Modified from (152).



2.7 Blood sampling

Thirty millilitres of blood was drawn for biochemical and haematological hospital laboratory analyses. Blood electrolytes, urea, creatinine, glucose, and haemoglobin were measured. Plasma brain natriuretic peptide (BNP) was measured using a one step radio immunoassay (ShionoRIA, Shinogi, Japan) after centrifugation of 6 mls of blood (this was frozen within 20 minutes of collection and stored at -70°C until measurement). Plasma total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein and high sensitivity C-reactive protein (CRP) were measured using standard biochemical methods.

2.8 Patient follow up

Follow- up data, including patient clinical events and deaths, were recorded from date of CMR scan until 30th September 2009 using the Western Infirmary, Glasgow and Glasgow Royal Infirmary electronic patient records.

Chapter 3

A study of independent predictors of uraemic cardiomyopathy in haemodialysis patients.

3.1 INTRODUCTION

As discussed in the introduction, patients with end stage renal disease (ESRD), particularly those receiving dialysis have an increased risk of premature CV disease (1). The features of uraemic cardiomyopathy, namely LVH, LVSD, and LV dilatation independently predict poorer survival in ESRD patients (47).

Studies to date assessing independent predictors of uraemic cardiomyopathy have used echocardiography. Such studies implicate factors such as hypertension, reduced blood vessel compliance, anaemia, phosphate control and dose of dialysis (134;163-165). In addition, gadolinium enhanced CMR findings indicating previous myocardial ischaemia have been associated with LVSD (139).

However, as discussed before, echocardiography provides an inaccurate assessment of LVMI and chamber size particularly in fluid overloaded patients where image acquisition and measurements of LV wall thickness (e.g. posterior and interventricular septum) can be difficult. Measurements obtained by echocardiography tend to overestimate LV mass particularly at higher values when compared to CMR (135). Few studies have used accurate, volume independent, measurements obtained from CMR to assess individual predictors of uraemic cardiomyopathy.

Thus the aims of the following study were to demonstrate the predictors of LVH, LVSD and LV dilatation, measured by CMR, in a cohort of haemodialysis (HD)

patients. In particular past dialysis and blood data, in addition to CMR features, were included in the analyses.

3.2 METHODS

3.2.1 CMR acquisition

Only ESRD patients receiving thrice weekly haemodialysis therapy were recruited into the study. Scans were consistently performed on the day after an HD session. CMR scans were acquired and analysed as previously described. Definitions for LVH, LVSD and LV dilatation have been presented in Chapter 2.

3.2.2 Demographic, dialysis and blood data acquisition

Demographic information and clinical (including drug) history were recorded at the time of CMR. Retrospective review of the electronic patient record was performed to retrieve biochemical and haematological blood results. Haemodialysis information including immediate pre (preHD) and post (postHD) dialysis systolic and diastolic blood pressure (SBP and DBP respectively); dose of ultrafiltration (UF) and dialysis adequacy using urea reduction ratio (URR) were also collected. Information was collected at 30 day intervals up to 180 days before CMR and mean results were calculated. Calcium phosphate product (Ca x PO4) was calculated from blood results collected. URR ratio was calculated using established protocol (166).

3.2.3 Statistical analyses

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc. Illinois, USA). Correlations between LV measurements and other factors were evaluated by Pearson's and Spearman's correlation coefficient as appropriate. Variables identified by univariate linear regression analyses as significant predictors were entered into a backward stepwise linear regression model to identify independent predictors of LVMI, ejection fraction or end diastolic volume/BSA (EDV/BSA). Similarly, simple followed by multiple logistic regression analyses were performed to identify predictors of LVH, LVSD or LV dilatation. Due to significant interdependence, systolic or diastolic blood pressures and only one cardiac parameter (EDV/BSA, ESV/BSA, or ejection fraction) were entered into the model. The most predictive regression model was thus generated.

3.3 RESULTS

3.3.1 Patient demographics

Table 3.1 shows demographic, clinical, drug and blood result data for 246 patients who were studied and also highlights the accumulation of traditional cardiovascular risk factors within such a patient group. Data regarding dialysis and cardiac dimensions are also presented in Table 3.1.

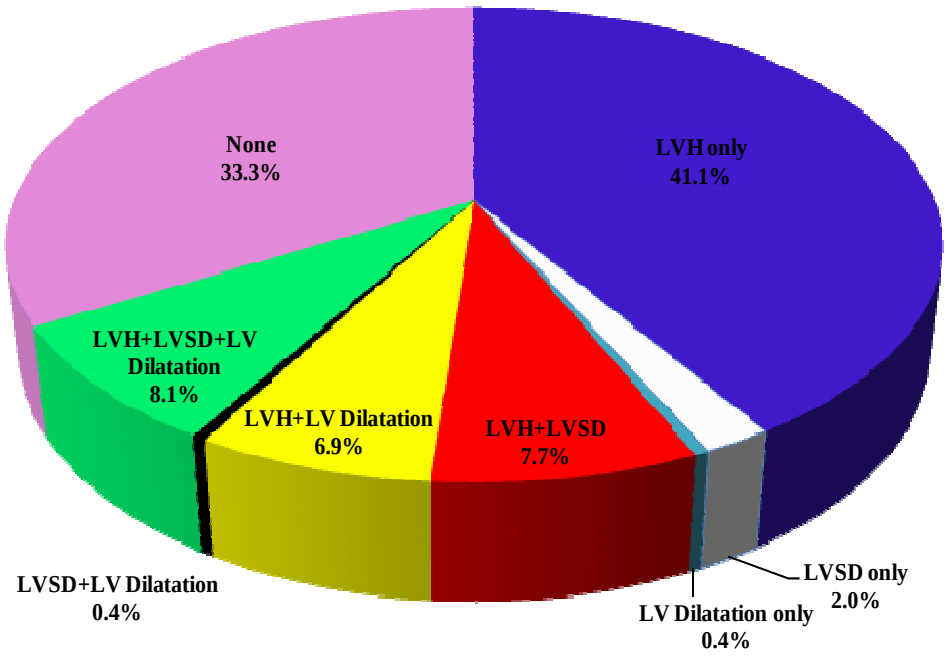
The frequencies of isolated and combined cardiac abnormalities are shown in Figure 3.1. One hundred and fifty seven (63.8%) had LVH, 45 (18.3%) had LVSD and 39 (15.9%) had LV dilatation. Eighty two patients (33.3%) had normal LV structure.

Variable		Total N=246	
Age (years)		**51.4**	**(±12.1)**
Male (%)		**157**	**(63.8)**
BMI (kg/m^2)		**25.6**	**(±4.6)**
Primary Renal Disease	**Diabetic Nephropathy**	**57**	**(23.2)**
	APCKD	**25**	**(10.2)**
	Glomerulonephritis	**52**	**(21.1)**
	Renovascular Disease	**19**	**(7.7)**
	Chronic Pyelonephritis	**26**	**(10.6)**
	Other	**38**	**(15.4)**
	Unknown	**29**	**(11.8)**
Diabetes mellitus		**156**	**(63.4)**
Ischaemic Heart Disease		**51**	**(20.7)**
Hypertension		**223**	**(90.7)**
Chronic heart failure		**15**	**(6.1)**
Cerebrovascular disease		**20**	**(8.1)**
Peripheral vascular disease		**18**	**(7.3)**
Hypercholesterolemia		**113**	**(46.3)**
Smoking	**Never**	**124**	**(50.4)**
	Current	**70**	**(28.5)**
	Ex	**52**	**(21.1)**
Aspirin		**97**	**(39.4)**
ACEI/ARB		**61**	**(24.8)**
Diuretic		**50**	**(20.3)**
Calcium Channel Antagonist		**73**	**(29.7)**
β Adrenoceptor Blocker		**106**	**(43.1)**
Epo receptor stimulating agent (ESA)		**196**	**(79.7)**
Vitamin D Analogue		**99**	**(40.2)**
Statin		**93**	**(62.2)**
Haemoglobin (g/dL)		**11.3**	**(±1.3)**
Adjusted Calcium (mmol/L)		**2.31**	**(±0.2)**
Phosphate (mmol/L)		**1.27**	**(±0.4)**
Albumin (g/dL)		**37.3**	**(±5.9)**
CaxPO4 Product		**2.93**	**(±1.0)**
Parathyroid Hormone (pmol/L)		**28.8**	**(20.3,34.0)**
Duration on HD (y)		**3.0**	**(±3.0)**
Mean Ultrafiltration Volume (L/session)		**2.2**	**(±1.1)**
Mean PreHD SBP (mmHg)		**142.3**	**(±21.8)**
Mean PostHD SBP (mmHg)		**132.3**	**(±23.1)**
Mean PreHD DBP(mmHg)		**79.8**	**(±14.0)**
Mean PostHD DBP(mmHg)		**73.3**	**(±13.8)**
Mean PreHD PP (mmHg)		**62.5**	**(±17.1)**
Mean PostHD PP (mmHg)		**58.9**	**(±17.6)**
Urea Reduction Ratio (%)		**70.8**	**(±7.5)**
Ejection Fraction %		**64.7**	**(±13.3)**
LVMI (g/m^2)		**99.4**	**(±30.0)**
EDV/BSA (ml/ m^2)		**77.8**	**(±31.1)**
ESV/BSA (ml/ m^2)		**29.6**	**(±21.9)**
LVH		**157**	**(63.8)**
LVSD		**45**	**(18.3)**
LV dilatation		**39**	**(15.8)**

Table 3.1 Demographic, clinical, drug, blood and cardiac data for patients. Data are number with percentage in parentheses or mean ± standard deviation except parathyroid hormone where median and interquartile range are shown.

Figure 3.1 Frequency of cardiac abnormalities of uraemic cardiomyopathy in cohort studied.

Note the high prevalence of LVH alone and in combination with other abnormalities



3.3.2 Left ventricular mass index and hypertrophy

3.3.2(a) Correlates of LVMI

There were strong positive correlations between LVMI and EDV/BSA (Pearson's R=0.60, p<0.01), ESV/BSA (Pearson's R =0.54, p<0.01) and negative correlation with LV ejection fraction (Pearson's R = - 0.37, p<0.01). In addition, there were weaker but significant correlations with mean dose of ultrafiltration (Pearson's R =0.18, p<0.01) and Ca x PO4 (Pearson's R =0.13, p=0.05). Factors close to statistical significance were postHD DBP (Pearson's R =0.13, p=0.06), and mean preHD SBP (Pearson's R =0.11, p=0.08).

3.3.2(b) Associations of left ventricular mass index and hypertrophy

Multivariable linear regression analysis was performed to create the most robust predictive model for LVMI (Table 3.2). Factors considered in the model were those identified as significant (or close) correlates with LVMI or factors identified from previous studies as predictors of LVMI. Using a backward stepwise model, the most significant model (highest R^2=0.49) generated included EDV/BSA, mean pre dialysis systolic blood pressure and Ca x PO4 product as significant predictors of LVMI.

Patients with or without LVH were compared. Higher preHD systolic blood pressure, preHD pulse pressure (PP) and Ca x PO4 were significantly associated with LVH (Table 3.3). Serum phosphate and mean UF dose were higher in the LVH group of patients, but were not statistically significant. When comparing both groups there were no significant differences in age, sex, body mass index (BMI), past cardiovascular history, duration on haemodialysis, mean post HD systolic and diastolic BP, mean pre HD diastolic BP and URR. Furthermore, LVH was not

significantly associated with a difference in mean haemoglobin, albumin, adjusted serum calcium, or parathyroid hormone (PTH) measured over the 180 days before CMR. There was no significant difference in drug usage between both groups. Table 3.3 also shows measured left ventricular cardiac parameters– ejection fraction, EDV/BSA and ESV/BSA. LVH was significantly associated with lower ejection fraction, higher end diastolic and systolic LV volumes, LVSD and LV dilatation.

Univariate followed by multivariate logistic regression analyses were performed to determine predictors of LVH (Table 3.4). Univariate analyses identified EDV/BSA, mean Ca x PO4 product and mean pre dialysis systolic BP as factors significantly associated with presence of LVH. Multivariate logistic regression modelling (only entering one BP variable and cardiac parameter due to their significant interdependence) similarly identified EDV/BSA, pre dialysis systolic BP, and CaxPO4 as the most robust (R^2=0.50) independent predictors of LVH.

	Standardised coefficient	p	95% CI for β
	β		
R^2=0.49, p<0.01			
Constant	- 13.5	0.40	-45.33, 18.3
EDV/BSA(ml/m2)	0.66	<0.01	0.36, 0.91
Mean PreHD SBP (per mmHg)	0.13	0.01	0.09, 0.42
Ca x PO4 product($mmol^2/l^2$)	0.16	<0.01	0.11, 0.24

Table 3.2 Backward stepwise multivariate linear regression analyses model demonstrating independent associations of LVMI (R^2= 0.49).

Variables entered into the model were, age, cardiac parameters (individually), mean calcium phosphate product, mean haemoglobin, mean albumin, mean parathyroid hormone, mean dose of UF per dialysis session, duration on renal replacement therapy and pre or post HD systolic or diastolic BP (individually)

	No LVH n=89	LVH n=157	p
Age (years)	51.8(12.2)	51.2(12.1)	0.20
Male (%)	55(61.8)	102(65.0)	0.62
BMI (kg/m^2)	25.2(4.2)	25.8(4.8)	0.45
Ischaemic Heart Disease	21(23.6)	30(19.1)	0.40
Diabetes Mellitus	58 (65.2)	98(62.4)	0.67
Chronic Heart Failure	5(5.6)	10(6.4)	0.81
Cerebrovascular Disease	10 (11.2)	10(6.4)	0.18
Peripheral Vascular Disease	7(7.9)	11(7.0)	0.80
Hypertension	79(88.8)	144(91.4)	0.44
Duration on HD (y)	2.9(3.1)	3.0(2.9)	0.89
Mean UF Volume (L)	2.1(0.9)	2.3(1.2)	0.08
Mean PreHD SBP (mmHg)	138.1(24.3)	144.6(20.0)	0.02
Mean PostHD SBP (mmHg)	129.2(24.8)	133.8(21.9)	0.14
Mean PreHD DBP(mmHg)	79.1(16.4)	80.3(12.4)	0.52
Mean PostHD DBP(mmHg)	72.3(15.9)	73.9(12.5)	0.36
Mean PreHD PP (mmHg)	59.1(17.6)	64.4(16.5)	0.02
MAP PostHD PP (mmHg)	57.1(18.9)	60.0(16.8)	0.22
Urea Reduction Ratio (%)	67.6 (11.9)	70.7 (6.4)	0.64
Haemoglobin (g/dL)	11.3(1.5)	11.3(1.3)	0.95
Adjusted Ca (mmol/l)	2.29(0.2)	2.31(0.2)	0.61
Phosphate (mmol/l)	1.20(0.40)	1.32(0.5)	0.06
Ca x PO4 product	2.72(0.9)	3.05(1.0)	0.03
Albumin	37.9(6.1)	36.9(5.8)	0.24
PTH	34.3(13.4,48.3)	31.4(15.2,45.7)	0.54
Aspirin	38(42.7)	59(37.6)	0.43
ACEI/ARB	23(25.8)	38(24.2)	0.78
Diuretic	23(25.8)	27(17.2)	0.11
CCA	25(28.1)	48(30.6)	0.68
α Adrenoceptor blocker	9(10.1)	8(5.1)	0.14
β Adrenoceptor blocker	36 (40.4)	70(44.6)	0.53
ESA	74(83.1)	122(77.7)	0.46
Vitamin D analogue	35 (39.3)	64 (40.8)	0.83
Statin	42 (47.2)	51 (32.2)	0.09
Ejection Fraction (%)	68.5(7.9)	62.6 (15.1)	<0.01
LVMI (g/m^2)	67.2(10.8)	116.9 (31.3)	<0.01
EDV/BSA (ml/ m^2)	58.2(18.3)	88.7(34.7)	<0.01
ESV/BSA (ml/ m^2)	19.7(10.8)	36.5 (27.5)	<0.01
LVSD	6(6.7)	39 (24.8)	<0.01
LV dilatation	2 (2.2)	37 (23.6)	<0.01

Table 3.3 Comparisons between patients with and without LVH are shown.

Data are number with percentage in parentheses, mean ± standard deviation or median interquartile range for PTH. Tests of significance are t-test and Chi-square (parametric data) or Mann Whitney (non parametric data). Significant results are highlighted.

	Univariate Analyses			Multivariate analyses		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**P**
EDV/BSA (per ml/m^2)	**1.08**	**1.04,1.13**	**<0.01**	**1.06**	**1.04,1.08**	**<0.01**
Mean Ca x PO4 (per mmol^2/l^2)	**1.37**	**1.01,1.87**	**0.04**	**1.74**	**1.17,2.57**	**<0.01**
Mean PreSBP (per mmHg)	**1.02**	**1.01,1.05**	**0.04**	**1.02**	**1.01,1.04**	**0.01**
Age (per year)	**0.99**	**0.99,1.02**	**0.70**			
Sex (Male vs. Female)	**1.55**	**0.91,2.65**	**0.11**			
BMI (per kg/m^2)	**0.96**	**0.89,1.03**	**0.27**			
HD duration (per year)	**1.01**	**0.85,1.20**	**0.88**			
Ischaemic Heart Disease	**1.34**	**0.67,2.60**	**0.38**			
Diabetes Mellitus	**1.20**	**0.69,2.60**	**0.52**			
Chronic Heart Failure	**0.88**	**0.28,2.72**	**0.82**			
Cerebrovascular Disease	**2.76**	**0.96,6.93**	**0.09**			
Peripheral Vascular Disease	**0.83**	**0.29,2.42**	**0.74**			
UF volume (per litre)	**1.26**	**0.95,1.66**	**0.11**			
Urea Reduction Ratio (per %)	**1.06**	**0.91,1.23**	**0.45**			
Mean Post SBP (per mmHg)	**0.99**	**0.97,1.02**	**0.55**			
Mean PreDBP (per mmHg)	**0.98**	**0.95,1.01**	**0.21**			
Mean PostDBP (per mmHg)	**1.01**	**0.98,1.04**	**0.49**			
Mean Pre PP (per mmHg)	**1.02**	**1.01,1.05**	**0.05**			
Mean Post PP (per mmHg)	**0.99**	**0.97,1.01**	**0.47**			
Ejection fraction (per %)	**0.95**	**0.88,1.03**	**0.21**			
ESV/BSA (per ml/m^2)	**0.93**	**0.85,1.02**	**0.12**			
Mean Haemoglobin (per g/dL)	**0.86**	**0.60,1.23**	**0.41**			
Mean Adjusted Ca (per mmol/l)	**1.61**	**0.35,7.48**	**0.54**			
Mean Serum PO4 (per mmol/l)	**2.10**	**1.00,4.29**	**0.06**			
Mean Albumin (per g/dL)	**1.00**	**0.96,1.05**	**0.91**			
Mean PTH (per pmol/l)	**0.99**	**0.99,1.01**	**0.54**			

Table 3.4 Simple (left) followed by backward stepwise (conditional) multiple logistic regression analyses (R^2=0.50) demonstrating independent predictors of presence of LVH.

Only variables found to be significant on univariate analyses were entered into the multivariate model. Cardiac and blood pressure parameters were entered individually to generate the most predictive model.

3.3.3 LV ejection fraction and systolic dysfunction

3.3.3(a) Correlates with LV ejection fraction

LV ejection fraction was used as an indicator of left ventricular function. In addition to the correlates demonstrated above, there were strong negative correlations with ESV/BSA (Pearson's R= -0.84; $p<0.01$) and EDV/BSA (Pearson's R= -0.53; $p<0.01$) as expected. There was a weak negative correlation with dose of ultrafiltration during dialysis (Pearson's R= -0.18; $p<0.01$).

3.3.3(b) Associations of LV ejection fraction and LV systolic dysfunction

As before, backward stepwise multivariate linear regression analyses were performed (Table 3.5). Factors considered influential based on initial evaluation of correlation data or identified from previous studies as predictors of LV function were entered into the model. End systolic volume corrected for BSA and pre HD systolic BP were the significant independent predictors of LV ejection fraction (R^2=0.76).

In patients with LVSD, there was a significantly higher proportion of patients with a past medical history of ischaemic heart disease and symptomatic heart failure (Table 3.6) compared to those with normal LV function. In addition, mean dose of UF, pre HD diastolic blood pressure and therapy with aspirin were significantly higher in LVSD patients. As expected from correlations with ejection fraction, LVSD was significantly associated with higher LVMI, EDV/BSA, and ESV/BSA.

Logistic regression analyses were performed to determine predictors of LVSD (Table 3.7). Univariate analyses identified ESV/BSA, EDV/BSA, LVMI, past

history of ischaemic heart disease, symptomatic chronic heart failure, duration receiving haemodialysis therapy, and mean dose of ultrafiltration as significant predictors of LVSD on CMR. Multivariate logistic regression analyses was performed entering significant factors from univariate analyses and the most predictive model (R^2=0.43) included ESV/BSA, past history of ischaemic heart disease and mean dose of UF.

	Standardised coefficient	p	95% CI for β
	β		
R^2=0.76, p<0.001			
Constant	89.6	<0.01	75.5, 103.6
ESV/BSA(ml/m2)	-0.80	<0.01	-1.46, -0.29
Mean PreHD SBP (per mmHg)	-0.17	0.05	-0.29, -0.06

Table 3.5 Backward stepwise multivariate linear regression analyses to identify independent predictors of LV ejection fraction (R^2= 0.76).

Variables entered into the model were age, cardiac parameters (individually), mean calcium, mean phosphate, mean haemoglobin, mean albumin, mean parathyroid hormone, mean dose of UF per dialysis session, duration on renal replacement therapy, pre or post HD systolic or diastolic BP (individually).

	No LVSD n=201	LVSD n=45	p
Age (years)	51.1 (11.8)	52.3(13.5)	0.37
Male (%)	124(61.7)	33 (73.3)	0.62
BMI (kg/m^2)	25.8 (4.6)	24.8(4.1)	0.14
Ischaemic Heart Disease	37 (18.4)	17 (37.8)	<0.01
Diabetes Mellitus	130 (64.7)	26 (57.8)	0.35
Chronic Heart Failure	8 (4.0)	5 (11.1)	0.05
Cerebrovascular Disease	17 (8.5)	3 (6.7)	0.69
Peripheral Vascular Disease	12 (6.0)	6 (13.3)	0.09
Hypertension	181 (90.0)	42 (93.3)	0.49
Duration on HD (y)	2.88(3.7)	4.30 (7.2)	0.06
Mean UF Volume (L)	2.1(1.1)	2.7 (0.7)	<0.01
Mean PreHD SBP (mmHg)	141.4(21.8)	146.0 (21.5)	0.20
Mean PostHD SBP (mmHg)	131.6(23.5)	135.6(21.0)	0.29
Mean PreHD DBP(mmHg)	78.8(13.9)	83.6(13.8)	0.04
Mean PostHD DBP(mmHg)	72.6 (13.9)	83.3(13.8)	0.20
Mean PreHD PP (mmHg)	62.5(17.5)	62.4(15.2)	0.96
MAP PostHD PP (mmHg)	58.9(17.9)	59.1(15.3)	0.94
Urea Reduction Ratio (%)	70.7(7.1)	68.0(9.3)	0.49
Haemoglobin (g/dL)	11.4(1.4)	11.0(1.3)	0.12
Adjusted Ca (mmol/l)	2.31(0.2)	2.32(0.3)	0.77
Phosphate (mmol/l)	1.25 (0.4)	1.35(0.5)	0.21
Ca x PO4 product	2.95 (1.0)	2.88(0.9)	0.72
Albumin	37.1(6.2)	38.2(4.7)	0.31
PTH	32.7(11.6,45.3)	31.7(14.2,53.7)	0.87
Aspirin	17 (35.3)	26 (57.8)	<0.01
Warfarin	8 (4.0)	3 (6.7)	0.43
ACEI/ARB	47 (23.4)	14 (31.1)	0.27
Diuretic	42 (20.9)	8 (17.8)	0.64
CCA	58 (28.9)	15 (33.3)	0.55
α Adrenoceptor blocker	14 (7.0)	3 (6.7)	0.14
β Adrenoceptor blocker	85 (42.3)	21 (46.7)	0.59
ESA	157 (78.1)	39 (86.7)	0.19
Vitamin D analogue	80(39.8)	19(45.2)	0.28
Statin	73 (36.3)	20 (44.4)	0.31
Ejection Fraction %	67.1(10.9)	52.0(17.3)	<0.01
LVMI (g/m^2)	94.3(31.1)	122.8(50.5)	<0.01
EDV/BSA (ml/ m^2)	72.7(26.8)	100.9(38.6)	<0.01
ESV/BSA (ml/ m^2)	25.1(16.7)	49.6(30.4)	<0.01
LVH	118 (58.7)	39 (86.7)	<0.01
LV dilatation	18 (9.0)	21 (46.7)	<0.01

Table 3.6 Comparisons between patients with and without LVSD

Data are number with percentage in parentheses or mean ± standard deviation or median and interquartile range. Tests of significance are t-test and Chi-square.

	Univariate Analyses			Multivariate analyses		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**P**
ESV/BSA (per ml/m^2)	**1.05**	**1.03,1.06**	**<0.01**	**1.07**	**1.04,1.10**	**<0.01**
Ischaemic Heart Disease	**2.62**	**1.33,5.42**	**<0.01**	**4.68**	**1.60,13.7**	**<0.01**
UF volume (per litre)	**1.47**	**1.05,2.08**	**0.03**	**2.06**	**1.02,1.06**	**0.03**
EDV/BSA (per ml/m^2)	**1.03**	**1.02,1.04**	**<0.01**			
LVMI (per g/m^2)	**1.01**	**1.01,1.03**	**<0.01**			
HD duration (per year)	**1.03**	**1.01,1.06**	**0.04**			
Chronic Heart Failure	**4.44**	**1.52,12.9**	**<0.01**			
Mean Albumin (per g/dL)	**1.14**	**1.01,1.28**	**0.10**			
Age (per year)	**1.02**	**0.98,1.04**	**0.38**			
Sex (ref Female)	**1.78**	**0.83,3.51**	**0.15**			
Diabetes Mellitus	**0.74**	**0.38,1.44**	**0.39**			
BMI (per kg/m^2)	**0.95**	**0.85,1.05**	**0.31**			
Cerebrovascular Disease	**0.78**	**0.22,2.76**	**0.69**			
Peripheral Vascular Disease	**2.42**	**0.85,6.84**	**0.09**			
Urea Reduction Ratio (per %)	**1.06**	**0.95,2.07**	**0.76**			
Mean PreSBP (per mmHg)	**1.00**	**0.97,1.03**	**0.82**			
Mean Post SBP (per mmHg)	**1.01**	**0.98,1.04**	**0.63**			
Mean PreDBP (per mmHg)	**1.02**	**0.98,1.06**	**0.37**			
Mean PostDBP (per mmHg)	**1.00**	**0.96,1.05**	**0.86**			
Mean Pre PP (per mmHg)	**1.00**	**0.97,1.03**	**0.89**			
Mean Post PP (per mmHg)	**1.00**	**0.97,1.03**	**0.88**			
Mean Haemoglobin (per g/dL)	**0.79**	**0.51,1.21**	**0.79**			
Mean Adjusted Ca (per mmol/l)	**0.18**	**0.01,6.14**	**0.34**			
Mean Serum PO4 (per mmol/l)	**0.93**	**0.26,3.25**	**0.92**			
Mean Ca x PO4 (per mmol^2/l^2)	**1.30**	**0.44,3.81**	**0.63**			
Mean PTH (per pmol/l)	**1.00**	**0.98,1.02**	**0.94**			

Table 3.7 Simple (left) followed by backward stepwise (conditional) multiple logistic regression analyses (R^2=0.43) demonstrating independent predictors of presence of LVSD.

Only variables found to be significant on univariate analyses were entered into the multivariate model. Cardiac parameters were entered individually to generate the most predictive model.

3.3.4 End diastolic volume/BSA and left ventricular dilatation

3.3.4(a) Correlates with EDV/BSA

EDV/BSA was used to define LV chamber volume and LV dilatation. EDV/BSA was positively correlated with LVMI (Pearson's R=0.63; p<0.01) and ESV/BSA (Pearson's R=0.84; p<0.01) and negatively correlated with LV ejection fraction as mentioned before. There was a weaker correlation with mean dose of UF (Pearson's R=0.22; p<0.01).

3.3.4(b) Associations of EDV/BSA and LV dilatation

Multiple backward stepwise linear regression analyses were also performed to provide the most predictive (R^2=0.47) model of EDV/BSA. Independent predictors of EDV/BSA were LV ejection fraction and mean dose of UF during dialysis (Table 3.8).

Patients with and without LV dilatation were compared (Table 3.9). Presence of LV dilatation was significantly associated with higher dose of UF during haemodialysis therapy. As demonstrated before, LV dilatation was significantly associated with higher LVMI (and presence of LVH), end diastolic and systolic LV volumes and lower ejection fraction (and presence LVSD). Independent predictors of presence of LV dilatation were left ventricular ejection fraction and mean dose of ultrafiltration during haemodialysis (Table 3.9).

	Standardised coefficient	p	95% CI for β
	β		
R^2=0.47, p<0.001			
Constant	143.6	<0.01	111.8, 175.4
LV ejection fraction (per %)	-0.49	<0.01	-0.64, ,-0.22
Mean Ultrafiltration (per L)	0.16	0.05	0.10, 0.78

Table 3.8 Backward stepwise multivariate linear regression analyses model demonstrating independent associations of EDV/BSA (R^2= 0.47).

Variables entered into the model were, age, cardiac parameters (individually), mean calcium, mean phosphate, mean haemoglobin, mean albumin, mean parathyroid hormone, mean dose of UF per dialysis session, duration on renal replacement therapy, pre or post HD systolic or diastolic BP (individually).

	No LV Dilatation N=207	LV Dilatation N=39	P
Age (years)	**51.5(12.1)**	**50.9(12.2)**	**0.77**
Male (%)	**130 (62.8)**	**27 (69.2)**	**0.44**
BMI (kg/m^2)	**25.7(4.7)**	**25.2(3.6)**	**0.65**
Ischaemic Heart Disease	**43 (20.8)**	**8 (20.5)**	**0.97**
Diabetes Mellitus	**133 (64.3)**	**23 (59.0)**	**0.53**
Chronic Heart Failure	**11 (5.3)**	**4 (10.3)**	**-**
Cerebrovascular Disease	**17 (8.2)**	**3 (7.7)**	**-**
Peripheral Vascular Disease	**16 (7.7)**	**2 (5.1)**	**-**
Hypertension	**186 (89.9)**	**37 (94.9)**	**0.32**
Duration on HD (y)	**4.98 (6.8)**	**5.96 (6.7)**	**0.45**
Mean UF Volume (L)	**2.1(1.1)**	**2.8(0.7)**	**<0.01**
Mean PreHD SBP (mmHg)	**142.7(22.2)**	**139.7(18.3)**	**0.43**
Mean PostHD SBP (mmHg)	**132.4(24.0)**	**139.7(18.3)**	**0.81**
Mean PreHD DBP(mmHg)	**79.5(14.1)**	**131.2(17.3)**	**0.59**
Mean PostHD DBP(mmHg)	**73.5(13.9)**	**72.2(13.9)**	**0.74**
Mean PreHD PP (mmHg)	**63.1(17.6)**	**58.9(13.3)**	**0.15**
MAP PostHD PP (mmHg)	**58.9(18.2)**	**58.8(14.0)**	**0.96**
Urea Reduction Ratio (%)	**71.8(34.5)**	**76.9(33.3)**	**0.76**
Haemoglobin (g/dL)	**11.3 (1.4)**	**11.1(1.2)**	**0.33**
Adjusted Ca (mmol/l)	**2.31(0.2)**	**2.31(0.3)**	**0.99**
Phosphate (mmol/l)	**1.28 (0.4)**	**1.22(0.4)**	**0.48**
Ca x PO4 product	**2.94(0.9)**	**2.90(1.1)**	**0.83**
Albumin	**37.3(5.9)**	**37.3(6.2)**	**0.94**
PTH	**32.5(12.6,45.3)**	**31.5 (12.0,43.7)**	**0.98**
Aspirin	**84 (40.6)**	**13 (33.3)**	**0.40**
Warfarin	**8 (3.9)**	**3 (7.7)**	**-**
ACEI/ARB	**52 (25.1)**	**9 (23.1)**	**0.79**
Diuretic	**45 (21.7)**	**5 (12.8)**	**0.20**
CCA	**61 (29.5)**	**12 (30.8)**	**0.87**
α Adrenoceptor blocker	**16 (7.7)**	**1 (2.6)**	**-**
β Adrenoceptor blocker	**89 (43.0)**	**17 (43.6)**	**0.95**
ESA	**162(78.3)**	**34 (87.2)**	**0.20**
Vitamin D analogue	**85 (41.1)**	**14 (35.9)**	**0.55**
Statin	**80 (38.6)**	**13 (33.3)**	**0.53**
Ejection Fraction %	**68.3(0.7)**	**45.6(13.3)**	**<0.01**
LVMI (g/m^2)	**93.4(31.8)**	**131.6(45.4)**	**<0.01**
EDV/BSA (ml/ m^2)	**70.1(23.2)**	**118.5(36.3)**	**<0.01**
ESV/BSA (ml/ m^2)	**22.5(12.0)**	**67.1(25.0)**	**<0.01**
LVH	**120 (58.0)**	**37(94.9)**	**<0.01**
LVSD	**24 (11.6)**	**21 (53.8)**	**<0.01**

Table 3.9 Comparisons between patients with and without LV dilatation.

Data are number with percentage in parentheses, mean ± standard deviation or median interquartile range for PTH. Tests of significance are t-test and Chi- square (parametric data) or Mann Whitney (non parametric data).

	Univariate Analyses			Multivariate analyses		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**P**
Ejection fraction (per %)	**0.86**	**0.83,0.90**	**<0.01**	**0.87**	**0.83, 0.91**	**<0. 01**
UF volume (per litre)	**1.73**	**1.18,2.54**	**<0.01**	**1.53**	**1.09, 2.17**	**0.01**
LVMI (per g/m^2)	**1.03**	**1.02,1.04**	**<0.01**			
Mean PreSBP (per mmHg)	**0.97**	**0.95,1.00**	**0.08**			
Age (per year)	**0.99**	**0.97, 1.02**	**0.77**			
Sex (Male vs. Female)	**0.75**	**0.36,1.57**	**0.44**			
BMI (per kg/m^2)	**0.98**	**0.86,1.08**	**0.65**			
HD duration (per year)	**1.02**	**0.97, 1.08**	**0.45**			
Ischaemic Heart Disease	**0.98**	**0.41, 2.37**	**0.97**			
Diabetes Mellitus	**0.81**	**0.40,1.65**	**0.81**			
Chronic Heart Failure	**2.15**	**0.63, 7.36**	**0.22**			
Cerebrovascular Disease	**1.00**	**0.27, 3.74**	**0.99**			
Peripheral Vascular Disease	**0.57**	**0.12, 3.74**	**0.49**			
Urea Reduction Ratio (per %)	**1.56**	**0.76, 7.89**	**0.57**			
Mean Post SBP (per mmHg)	**1.02**	**0.99, 1.05**	**0.23**			
Mean PreDBP (per mmHg)	**1.04**	**1.00, 1.08**	**0.06**			
Mean PostDBP (per mmHg)	**0.97**	**0.93,1.01**	**0.19**			
Mean Pre PP (per mmHg)	**0.97**	**0.95,1.00**	**0.05**			
Mean Post PP (per mmHg)	**1.02**	**0.99-1.05**	**0.20**			
Mean Haemoglobin (per g/dL)	**0.86**	**0.65, 1.12**	**0.33**			
Mean Adjusted Ca (per mmol/l)	**3.48**	**0.48, 26.5**	**0.23**			
Mean Serum PO4 (per mmol/l)	**0.62**	**0.22, 1.75**	**0.36**			
Mean Ca x PO4 (per mmol^2/l^2)	**0.96**	**0.66, 1.40**	**0.83**			
Mean Albumin (per g/dL)	**1.00**	**0.94, 1.07**	**0.99**			
Mean PTH (per pmol/l)	**1.00**	**0.99, 1.02**	**0.98**			

Table 3.10 Simple (left) followed by backward stepwise (conditional) multiple logistic regression analyses (R^2=0.55) demonstrating independent predictors of presence of LV dilatation.

Only variables found to be significant on univariate analyses were entered into the multivariate model. Cardiac parameters were entered individually to generate the most predictive model.

3.4 DISCUSSION

Uraemic cardiomyopathy describes a heterogeneous group of cardiac abnormalities that are very common in patients close to or receiving RRT (167;168). However, our understanding of its aetiology and thus identification of therapies to prevent, slow or reverse its development have proven difficult. Our current understanding is derived from echocardiography which is inaccurate when estimating LV chamber size and wall thickness in ESRD patients.

3.4.1 Development of uraemic cardiomyopathy

The development of uraemic cardiomyopathy is believed to be initiated and perpetuated by elevated cardiac preload and afterload (see Table 3.11) (169;170). LVH develops as an adaptive response to maintain stroke volume and minimise ventricular wall stress in the face of volume and pressure overload which are common in advancing stages of CKD. Both of these changes increase LV wall tension due to Laplace's Law (170; 171):

$$T = \frac{PD}{4}$$

T = LV wall tension, P= intraventricular pressure, D= LV internal diameter

Volume overload causes myocardial stretch, stimulating sarcomere proliferation in series and elongating pre-existing fibres to maintain stroke volume. This manifests as eccentric ventricular remodelling and LV dilatation. Wall tension rises increasing oxygen requirements of cardiomyocytes and subsequent risk of ischaemia (170;171).

Preload	Afterload
Intravascular volume expansion	Systemic Hypertension
Arteriovenous fistula	Calcific Aortic Stenosis
Anaemia	Vascular calcification

Table 3.11 Causes of increased preload and afterload in ESRD patients - modified from (170)

Systemic hypertension, on the other hand, increases cardiac afterload and stimulates sarcomere production in parallel resulting in LV wall thickening with preservation or reduction of chamber size. The ventricle is remodelled in a uniform and concentric pattern.

Thus, wall tension increases as intraventricular pressure (systemic hypertension, aortic stenosis) and intraventricular diameter (fluid overload) rise. Adaptive responses are implemented to reduce wall stress (defined as T: cross sectional area of LV) redistributing work over a larger area and reducing energy consumption per muscle fibre.

However, as the LV wall thickens, inadequate angiogenesis reduces capillary density, myocardial reserve and subsequently leads to myocyte ischaemia, death and reparative myocardial fibrosis. This reduces contractile function per unit volume of myocardium and eventually causes symptomatic left ventricular failure. Myocyte death is also facilitated by poor dialysis, poor nutrition and hyperparathyroidism, which are common in ESRD (134;171).

Not all structural abnormalities have been attributed to these haemodynamic factors. Higher levels of interstitial myocardial fibrosis have been demonstrated in autopsy sections from dialysis patients when compared to hypertensive and diabetic patients (50). Furthermore, in vivo studies have demonstrated a potential role of angiotensin II, aldosterone, PTH, catecholamines, and endothelin stimulating cardiac interstitial fibroblasts (61;172).

3.4.2 Predictors of uraemic cardiomyopathy on CMR

This study is the first to use CMR to define individual abnormalities of uraemic cardiomyopathy in a cohort of haemodialysis patient and use past clinical, blood and dialysis data, collected over 180 days prior to scanning, to assess the trends that predict presence of LVH, LVSD and LV dilatation.

In ESRD patients, the presence of one myocardial abnormality is predictive of other features of uraemic cardiomyopathy. Figure 3.1 demonstrated that abnormalities often occur in combination and correlation analyses for cardiac parameters demonstrated significant relationships between all LV measurements. In our regression analyses, only the most predictive models were presented after adding one cardiac abnormality. However, when other cardiac abnormalities were included (e.g. ejection fraction for LVMI) similarly significant but less robust models were generated. Given the close association of cardiac abnormalities in patients with uraemic cardiomyopathy and the processes described above, it is likely that different combinations of structural changes represent varying stages of the same adaptive/disease process.

In addition, this study demonstrates that clinical, blood and dialysis features previously proposed as predictors of uraemic cardiomyopathy detected by echocardiography, are not associated with LV abnormalities detected by CMR.

3.4.2 Predictors of LVH

LVH is the most common abnormality of uraemic cardiomyopathy and is estimated to be present in approx 67% of haemodialysis patients assessed by CMR. A cross sectional study of patients with varying degrees of CKD demonstrated a progressive increase in the prevalence of LVH with deteriorating renal function (173). LVH has been demonstrated as an independent predictor of heart failure, ventricular tachyarrhythmia and sudden cardiac death (47). These data show that LVH assessed by CMR is common (63.8%) but is lower than previous echocardiography studies highlighting the tendency for echocardiography to overestimate LV mass in ESRD patients (132; 139). These data also show that both LVMI and presence of LVH are associated with, and independently predicted by elevated end diastolic LV volume, pre-dialysis systolic blood pressure and Ca x PO4 product.

3.4.2(a) Hypertension and LVH

A number of different studies, using echocardiography, have demonstrated a significant association between LVH and hypertension:

- Harnett at al studied haemodialysis patients with progressive LVH. They demonstrated that age and pre-dialysis systolic blood pressure were associated with increased LV mass (174).

- Parfrey et al showed in 432 patients with a median of 3.3 months from starting haemodialysis, that presence of concentric LV hypertrophy was independently predicted by systolic blood pressure and female gender (47).

  Data from this thesis using CMR assessment support earlier studies suggesting that systolic hypertension acts as a major determinant of cardiac afterload and thus significantly predicts LVMI and presence of LVH.

  Previous studies have demonstrated that LVMI and dialysis BP measurements (pre- and post- HD) are usually only weakly (r=0,15-0.20) correlated (175). This is unsurprising given inaccuracies of blood pressure measurement at the time of dialysis. A number of studies have demonstrated that pre and post dialysis blood pressures provide misleading estimates and less reproducible measurements in haemodialysis patients.

- In a comparative study between dialysis and 48 hour ambulatory BP measurements (ABPM), Coomer et al demonstrated that predialysis BP overestimated mean intradialytic systolic BP by 10mmHg and post dialysis BP underestimated systolic measurements by 7mmg (176).
- Peixoto et al investigated 21 haemodialysis patients who had pre- and post-HD measurements compared with 2 separate 48 hours ABPM monitoring readings. Their results showed that ABPM provided less variable and more reproducible results (177).

Despite these studies, ABPM monitoring remains unpopular because the methodology is not universally available, time consuming and uncomfortable for dialysis patients. In this study, ABPM was offered to patients, but many refused as they did not wish to wear the monitor overnight.

The cause of hypertension in haemodialysis patients is multifactorial but is mostly due to volume overload (178). Elevated intravascular volume stimulates higher cardiac output (due to Starling's Law of the heart) and inappropriately increases systemic vascular resistance (believed to be caused by secretion of oubain like ATPase inhibitors which increase vascular smooth muscle intracellular Ca^{2+} concentration). In addition, inappropriate activation of the sympathetic nervous system by uraemic metabolites, vascular stiffness due to calcification, vasoconstriction caused by abnormal endothelial function and erythropoietin administration may contribute to elevated BP in ESRD patients (175).

3.4.2(b) Ca x PO4 product and LVH

Elevated Ca x PO4 product is a risk factor for arterial calcification and consequently contributes to elevated blood pressure and the development of LVH (60;179). It has been shown to be an independent predictor of cardiovascular and sudden death in patients with ESRD:

- In the Dialysis Outcomes and Practice Patterns Study (DOPPS), all cause and cardiovascular mortality was directly and independently predicted by serum calcium, phosphate, PTH and Ca x PO4 product(180).

- In a study of 134 patients (only 80 of these were receiving haemodialysis) assessed twice by multi slice spiral CT, independent predictors of mortality included elevation of vascular calcification score (181).

  Other measurements and markers of vascular calcification, such as pulse wave velocity and electron beam CT, have demonstrated an association with LVH in ESRD patients.

- Nitta et al investigated 49 haemodialysis patients using applanation tonometry to assess pulse wave velocity and abdominal CT to quantify aortic calcification index. LVMI was significantly correlated and independently predicted by both measurements (182).

3.4.2(c) End diastolic volume and LVH

In our study, EDV/BSA was the strongest predictor of LVMI and LVH after multivariate analyses supporting an association between elevated LV mass and long-term volume overload and ventricular stretch. In addition, brain natriuretic peptide, whose production is stimulated by myocardial stretch, has been used to predict presence of LVH in ESRD patients with sensitivities $\geq$ 87% (183). Unfortunately, we did not have samples available for measurement of BNP in this cohort.

3.4.2(d) Anaemia and LVH

Our study did not demonstrate a predictive role of haemoglobin concentration for LVMI. The potential aetiological role of anaemia in development of LVH remains uncertain in ESRD patients. In theory, haemodilution increases myocardial work to ensure adequate oxygenation of tissues resulting in hypervolaemia (±worsening hypertension) and increased cardiac preload. Studies using echocardiography have demonstrated a strong predictive role of anaemia in LVH:

- In a study of 51 dialysis patients studied by serial echocardiography, lower haemoglobin independently predicted LVMI. However only 8 of these patients were receiving erythropoietin therapy (184).
- Levin et al showed that left ventricular growth was independently predicted by haemoglobin concentration and systolic blood pressure in 246 dialysis patients (185).

These earlier studies, however, were performed before the routine use of erythropoietin to correct anaemia in patients receiving renal replacement therapy. Erythropoietin receptors are present in myocardial tissues and in vivo studies have demonstrated that stimulation alters cellular turnover (186). Studies demonstrating correction of moderate anaemia using erythropoietin stimulating agents have not shown significant reversal of LVH.

- In a 2009 meta-analysis pooling data from 15 studies with 1731 erythropoietin treated patients, regression of LVH was observed only in patients treated with severe anaemia (Hb<10g/dL) Patients with moderate anaemia (mean Hb≥10g/dL but <12

g/dL) had insignificant changes in LVMI. These findings were consistent in dialysis and predialysis patients (187).

The absence of significant association in our study is likely due to higher values and narrower range of haemoglobin in this cohort (mean haemoglobin = 11.3g/dl, standard deviation= 1.3) compared to other studies. In addition, echocardiography overestimates LVMI at lower haematocrit and higher intravascular volumes (135). Thus any therapy that reduces haemodilution (e.g. correction of anaemia) could provide artefactual reduction in LVMI measured by echocardiography. The use of CMR to assess change in LVMI after correction of anaemia in ESRD patients remains to be studied.

3.4.3 Predictors of LVSD

As in the general population, symptomatic heart failure predicts early mortality in ESRD patients and increasing severity, defined by the New York Heart Association (NYHA) classification, is associated with increased mortality:

- In a study from the United Stated Renal Database System comparing 310456 haemodialysis patients admitted to hospital for the first time with symptomatic heart failure, fluid overload or pulmonary oedema, 5- year survival rates were 12.5%, 20.2% and 21.3% respectively (188).
- Postorino et al demonstrated that NYHA classifications 1-4 were independently associated with increasingly poorer survival in ESRD patients (189).

Previous echocardiography studies have demonstrated differing prevalence of LVSD in ESRD patients (between 18-62%) (167;190). This variability is presumably due, in part, to the difficulty obtaining accurate and reproducible images in patients with varying intraventricular cavity diameters. However, data presented here are consistent with previous CMR studies in this patient cohort from our research group:

- In a pilot study using CMR to assess myocardial structure in 134 ESRD patients, Mark et al demonstrated LVSD prevalence of 8.2%, although this included peritoneal dialysis and predialysis patients (139).
- In a cross sectional study, LVSD was present in 15.6% of patients undergoing cardiovascular assessment for renal transplantation who underwent CMR (135; 191).

LVSD is more common in ESRD patients compared to the general population and has historically been attributed to the accumulation of traditional cardiovascular risk factors (192) including ischaemic heart disease, hypertension, older age, and anaemia. In addition, factors found only in ESRD patients have been shown to reduce LV function including chronic fluid overload, uraemia and calcific aortic stenosis (190).

3.4.3(a) LVSD and fluid retention

Our data show that lower LV ejection fraction and presence of LVSD are independently associated with higher ESV/BSA. As suggested previously, this is most likely due to intravascular volume expansion, elevated diastolic LV filling, inadequate LV systolic emptying and subsequent decompensated heart failure. Independent predictors of LVSD also included mean dose of ultrafiltration consistent

with a recent study that demonstrated an association between elevated interdialytic weight gain and adverse outcome:

- Data from a large (n=34107), retrospective study of haemodialysis patients investigated weight gain between dialysis sessions and outcome. Mortality was highest in patients with 3 month averaged interdialytic weight gain greater than 4kg and lowest in patients with gains less than 1kg. The investigators concluded that higher fluid retention (especially >4kg) was associated with greater all-cause and cardiovascular mortality independent of other co-morbid conditions (193).

It is impossible to determine whether elevated dose of ultrafiltration may be a cause or sequela of LVSD from the results presented above. Dose of ultrafiltration is calculated from a patients "dry weight" and determined by the nephrologist on the basis of his/her clinical assessment. However, this may not represent an accurate measure of patient's ideal oedema free, normotensive weight. More objective methods of assessing patients' fluid status and thus dose of ultrafiltration, such as bioelectrical impendance analysis and radionuclide tagging are currently being investigated to determine their effect on myocardial function and patient outcome (194).

3.4.3(b) LVSD and hypertension

These data demonstrate a close relationship between blood pressure and LV systolic function: higher pre-HD SBP was significantly associated with lower LV ejection fraction. This finding is in keeping with previous studies in the general population and ESRD patients:

- In the NHANES I follow up study in patients with congestive cardiac failure, hypertension was identified as an independent predictor of reduced LV ejection fraction and symptomatic chronic heart failure (195).
- Harnett et al demonstrated hypertension as an independent predictor of congestive cardiac disease in patients with ESRD. Diastolic blood pressure predicted presence of *de novo* and recurrent congestive heart failure (192).

3.4.3(c) LVSD and ischaemic heart disease

Consistent with other studies in the general population and ESRD patients, these data show that past history of symptomatic occlusive coronary disease independently predicted presence of LVSD. The definition of ischaemic heart disease included patients with history of myocardial infarction, coronary artery intervention (surgical or percutaneous) or current symptoms of angina pectoris. Mark et al previously showed that presence of LVSD is significantly associated with presence of subendocardial pattern of myocardial fibrosis highlighted by late gadolinium-diethylenetriamine- pentaacetic acid (Gd-DTPA) enhancement (LGE) on contrast CMR (139). Subendocardial LGE represents areas of previous (commonly silent) myocardial infarction and based on these results it was postulated that LVSD in uraemic cardiomyopathy is mostly due to CAD and myocardial ischaemia/infarction. These data support the association of ischaemic heart disease and LVSD in ESRD patients.

3.4.4 Predictors of LV dilatation

LV dilatation, when assessed by echocardiography, is common in haemodialysis patients with a prevalence reported between 28-36% in most cohorts (134). As

discussed previously, echocardiography provides inaccurate measurements of LV chamber size in fluid overloaded patients. In contrast, CMR assessment of our cohort demonstrated prevalence of LV dilatation at 15.9% of patients and is consistent with other CMR studies within this patient group (135). LV dilatation has previously been shown to be an independent predictor of death in ESRD patients:

- Parfrey et al demonstrated that presence of LV dilatation in patients assessed by echocardiography within a year of starting haemodialysis had a higher mortality after 2 years on ESRD therapy (HR=1.86; p=0.02). LV dilatation independently predicted death of patients in this cohort (47).
- Further analysis of these patients investigated LV geometry and outcome after 2 years on ESRD. The results separated the effect of LVH and LV dilatation on outcome. In patients with normal cavity size and preserved systolic function, high LV mass and mass: volume ratios were independently associated with late mortality. Cavity volume did not have any effect on mortality. In patients with elevated cavity size and preserved systolic function, high cavity size and *low* mass: volume ratios independently predicted death with LVMI having no effect on prognosis. The authors concluded that the effect of mass: volume ratio on patients survival was dependent on LV cavity size (134).

These data demonstrate that independent predictors of EDV/BSA and presence of LV dilatation were lower LV ejection fraction and higher mean doses of UF. As demonstrated before, fluid retention and its subsequent effect on LV function plays a pivotal role in determining myocardial abnormalities and it is most likely that poor LV ejection fraction and higher mean UF doses are aetiological and perpetuating

agents of LV dilatation. Thus, potential reversal of LV dilatation may involve attempts to improve LV function and more stringent adherence to fluid restriction in an attempt to break this cycle.

Other factors have been identified as predictors of LV dilatation assessed by echocardiography:

- In the two studies mentioned above, Foley et al demonstrated advancing age, male sex, low haemoglobin, serum calcium and albumin and high phosphate as independent risk factors for presence of LV dilatation (47;134).

This CMR study did not demonstrate such associations presumably highlighting the inaccurate estimation of LV chamber size in ESRD patients by echocardiography. In particular, the inclusion of haemoglobin and albumin are most likely the artefactual result of haemodilution, elevated intravascular volume, and imprecise measurement of chamber dimensions.

3.4.5 Modifying uraemic cardiomyopathy

Previous studies have identified potentially modifiable factors to reverse the abnormalities of uraemic cardiomyopathy and improve cardiovascular prognosis in ESRD patients. Unfortunately, these studies have had limited success due in part to the many facets of cardiovascular disease in ESRD patients and inaccuracy of echocardiography when measuring cardiac chamber dimensions.

Based on the data presented in this thesis, regression of uraemic cardiomyopathy in ESRD should be directed at reducing cardiac preload and afterload. The most amenable factors are:

- Blood pressure control
- Minimisation of fluid retention
- Aggressive management of bone mineral disorders and vascular calcification

Blood pressure control should be achieved in haemodialysis patients by maintenance of euvolaemia and anti-hypertensive medication. A number of promising studies have illustrated a reduction of LV mass using these interventions:

- In an early study, Wu et al investigated 39 patients on long term haemodialysis before and after treatment of blood pressure with regimens of ACE inhibitors, β-blockers, or calcium channel blocker. This significantly reduced the prevalence of LVH and LVSD. Responders, defined by a drop in mean arterial blood pressure ≥10 mmHg, had most regression of LVH (196).
- Studies that demonstrate improved BP control due to more frequent dialysis also demonstrate regression of LV mass. Fagugli et al (197) compared the effect of short daily dialysis or standard thrice weekly dialysis on blood pressure management and LVMI in 12 patients over a year. Blood pressures, LVMI and extracellular fluid were significantly lower in daily dialysis patients. LVMI was measured by echocardiography. More recently, a randomised controlled study using CMR to determine changes in LVMI was performed by Culleton et al (20) comparing standard haemodialysis regimen (n=25) and frequent (5-6times/week) nocturnal

haemodialysis (n=26). Results demonstrated a significant reduction in need for BP medication and LVMI. However, in both of these studies, investigators were unable to determine whether regression of LV mass was independent of blood pressure control.

Unfortunately there is a lack of studies that show a convincing improvement in myocardial function or LV dilatation in haemodialysis patients:

- In a small study (n=30) assessing cardiac chamber sizes before and after renal transplantation using echocardiography, Peteiro et al showed a trend towards euvolaemia as demonstrated by reduction of LV ESV and EDV but no improvement in LV systolic function (198).

Pharmacological intervention in dialysis patients may provide further survival benefit:

- *ACE I/ ARB.* Suzuki *et al* demonstrated a significant reduction in fatal and non fatal cardiovascular events in 360 hypertensive dialysis patients treated with ARBs (125).
- *Beta Blockers.* In 114 dialysis patients with dilated cardiomyopathy, treatment with carvedilol significantly reduced cardiovascular deaths and hospital admissions compared to placebo (120). In addition, a retrospective cohort study showed that beta blockers reduced the risk of new onset heart failure in ESRD patients (199).

Alterations in haemodialysis conditions may also improve myocardial function:

- Intradialytic hypotension and subsequent myocardial ischaemia, characterised by regional wall motion abnormalities (RWMA) on echocardiography, are recognised complications of haemodialysis therapy and are associated with LVSD and poorer survival (70). However, biofeedback dialysis (whereby significant reductions in blood pressure are counteracted by reducing ultrafiltration rates) and cooled dialysis (35°C rather than 37°C) are associated with a significant reduction of new intradialytic RWMA. The long term effect on prognosis of both of these interventions is awaited (72;73).

Despite these studies, pharmacological treatment of heart failure remains underutilised in ESRD patients. Data from the USRDS estimated that less than 25% of patients with ESRD and heart failure are treated with beta blockers or ACEI/ARBs (200). The use of beta blockers was higher in this cohort and is presumably a reflection of the extensive cardiovascular history and greater awareness of appropriate drug prescribing in these patients. However, as more well controlled and randomised studies are performed, medical management may change in the future.

3.4.6 Limitations of current study

The current study has some limitations. Data from haemodialysis patients only has been presented. This was due to the large amount of blood and dialysis data available for these patients from our electronic patient record. One would hope that the data presented here could be extrapolated to peritoneal and pre-dialysis patients. In addition, these patients were referred, by a nephrologist, for cardiovascular assessment and may not represent a cross section of all dialysis patients due to

referral bias. Finally no record of vascular access for haemodialysis was presented. Arterio- venous fistulae has previously been associated with development of LVH due to increased cardiac preload.

3.5 CONCLUSIONS

In conclusion, pathophysiological changes associated with advancing kidney disease (hypertension, vascular calcification, expanded intravascular volume) are implicated in the development of the early features of uraemic cardiomyopathy. These initially adaptive but subsequently pathological processes perpetuate the development of other cardiac abnormalities. In this study the strongest predictor of each abnormality was another cardiac measurement. Prevention may have to be achieved by more aggressive management of the aetiological factors in earlier stages of chronic kidney disease since LV abnormalities are very common in predialysis patients. Hopefully new guidelines that identify and allow treatment of cardiovascular risk factors in early chronic kidney disease (e.g. by aggressive blood pressure control) may reduce the development of uraemic cardiomyopathy.

Chapter 4

A study identifying predictors of cardiovascular death in ESRD patients undergoing screening for renal transplantation

4.1 INTRODUCTION

As discussed in the introduction, cardiovascular (CV) disease is the commonest cause of death in ESRD patients, including those on the renal transplant waiting list and those who have received a renal transplant. Premature CV death may be the result of high prevalence of conventional risk factors (such as hypertension, smoking, dyslipidaemia and diabetes mellitus) but the relationship between these risk factors and CVD is much less clear than in the general population (1;5). For example, lower blood pressure and cholesterol are related to adverse outcome in patients on haemodialysis. In addition, a number of non-traditional and uraemia specific risk factors (such as endothelial dysfunction, oxidative stress, volume overload, hyperparathyroidism) have been associated with adverse CV outcome.

Previous studies have assessed the effect of abnormal structure and function assessed by echocardiography on patient survival (47). However, there have been no studies using CMR to identify these abnormalities, which provides a more accurate, reproducible, volume independent method of measuring cardiac function and dimensions. In addition, as has been shown previously in this thesis, these CMR measured cardiac abnormalities commonly occur in combination. The Transplant Unit at the Western Infirmary, Glasgow has employed CMR for pre-transplant CV assessment since 2001.

The aims of this study were to determine whether:

- The features of uraemic cardiomyopathy defined by CMR, namely left ventricular hypertrophy (LVH), left ventricular systolic dysfunction (LVSD), and left ventricular dilatation (LV dilatation), predicted CV death.
- The accumulation of such cardiac abnormalities predicted CV death.
- These features act independently of other established CV risk factors such as past clinical history.

4.2 METHODS

4.2.1 Patient recruitment

Patients were recruited consecutively from the Western Infirmary, Glasgow as described in Chapter 2. To achieve greater statistical power, 123 patients assessed by Dr Patrick Mark were added to those assessed to provide a larger cohort of patients. However analyses were performed with blinding to patient outcome.

4.2.2 Cardiovascular assessment

All patients were recruited after referral from the transplant assessment team using criteria described in Chapter 2. As part of the screening visit, ECG was recorded and classified as "abnormal" by the investigator if one of following criteria were present in standard limb leads or pre-cordial leads, except AVR or V1:

- ST depression≥ 1mm or ST elevation≥ 1mm
- T wave inversion
- Left bundle branch block
- LVH by Sokolow-Lyon criteria or Cornell index

- Pathological Q waves.

CMR scans were acquired for assessment of LV mass and function and analysed as previously described. Patients were classified as having LVH, LVSD or LV dilatation based on previously described normal values. In addition the number of abnormalities was also recorded. Serum haemoglobin, corrected calcium and phosphate were measured on the day of screening.

4.2.3 Follow up

Data on patient outcome, including cause of death, were obtained from the date of CMR to 30th September 2009 using the EPR of the Western Infirmary, Glasgow and Glasgow Royal infirmary Renal Units. Deaths were categorised as "cardiovascular", "malignancy", "infective" and "unknown/other". Cause of death was reported by the attending nephrologist and recorded in the EPR.

Deaths were classified as CV if primary cause on the EPR was reported as:

- Myocardial ischaemia/infarction
- Cardiac arrhythmia
- Cardiac arrest (cause uncertain)
- Cardiac failure
- Sudden death at home- presumed cardiac
- Cerebrovascular accident

4.2.4 Statistical methods

Data are described as mean (±standard deviation) for normally distributed data or median (interquartile range) for non-normal data. Comparisons between patients who died and those that did not were performed by Student's t test (for normal data), Mann-Whitney U test (for non-normal data), Chi squared test or Fisher's exact test as appropriate.

Survival data including survival time (mean± standard deviation) are shown as Kaplan-Meier curves (with statistical comparison using the log rank test). These data were also analysed by Cox multivariate survival analysis to assess the influence of multiple clinical and cardiac variables on death. A transplant censored survival analyses was performed to remove the beneficial effect of renal transplantation on outcome (201;202). Variables identified as significantly influential on outcome by Cox univariate analysis were entered into a backward stepwise regression model. Left ventricular abnormalities (LVH, LVSD and LV dilatation) or the "number of abnormalities present" were entered individually into the model due to significant interdependence between these variables. All analyses were performed using SPSS v15.0 (SPSS Inc, Illinois, USA).

4.3 RESULTS

4.3.1 Patients demographics

Patient demographics are shown in Table 4.1. Between 1st January 2002 and 31st August 2009, 446 were recruited into the study. Mean age was 53.0±11.8years. Two hundred and thirty nine (53.6%) were receiving thrice weekly maintenance haemodialysis, 62 (13.9%) were on peritoneal dialysis, 134 (30.0%) were pre-dialysis (i.e. within 6 months of requiring renal replacement therapy), and 11 (2.5%) had failing renal transplants. The total follow up time was 7.6 years (median 4.0 years IQR 1.5, 5.7).

One hundred and fifty six patients (35.0%) had normal cardiac structure and function. Two hundred and seventy six patients (61.9%) had LVH, 85 (19.0%) had LVSD and 62 (13.9%) had LV Dilatation on CMR (Figure 4.1). The accumulation of these abnormalities was examined, 194 (43.5%) had one abnormality and 96 (21.5%) had 2 or 3 abnormalities. LVH only was the commonest single abnormality present (n=183, 41% of all patients) with only 11 (2.5%) patients having LVSD alone. Fifty nine (13.2%) patients had two abnormalities and 37 (8.3%) had all three.

Variable			Total N=446	% or ±SD
Deaths			**95**	**(21.3)**
Transplants			**114**	**(25.6)**
Age (years)			**53.0**	**(±11.8)**
Male (%)			**297**	**(66.6)**
Body Mass Index (kg/m^2)			**26.1**	**(±5.1)**
Primary Renal Diagnosis	**Diabetic Nephropathy**		**98**	**(22.0)**
	ADPCKD		**50**	**(11.2)**
	Glomerulonephritis		**88**	**(19.7)**
	Pyelonephritis		**41**	**(9.2)**
	Renovascular disease		**29**	**(6.5)**
	Unknown/Other		**140**	**(31.4)**
Systolic BP (mmHg)			**140.3**	**(±24.6)**
Diastolic BP (mmHg)			**81.8**	**(±13.2)**
RRT time (years)			**1.0**	**(2.1)**
RRT	**Haemodialysis**		**239**	**(53.6)**
	Peritoneal dialysis		**62**	**(13.9)**
	Pre-dialysis		**134**	**(30.0)**
	Failing Renal Transplant		**11**	**(2.5)**
Diabetes mellitus			**147**	**(32.9)**
Ischaemic Heart Disease			**90**	**(20.2)**
Hypertension			**412**	**(92.3)**
Cerebrovascular disease			**41**	**(9.2)**
Peripheral vascular disease			**42**	**(9.4)**
Smoking	**Never**		**219**	**(49.1)**
	Current		**125**	**(28.0)**
	Ex		**102**	**(22.9)**
Dylipidaemia			**195**	**(43.7)**
Ischaemic ECG			**151**	**(33.9)**
Ejection Fraction (%)			**64.9**	**(±13.3)**
Myocardial mass/BSA			**96.0**	**(±33.4)**
EDV/BSA (ml/ m^2)			**74.5**	**(±31.1)**
ESV/BSA (ml/ m^2)			**28.2**	**(23.0)**
LVSD (EF<55%)			**85**	**(19.0)**
LVH			**276**	**(61.9)**
LV dilatation			**62**	**(13.9)**
Number of abnormalities		**0**	**156**	**(35.0)**
		1	**194**	**(43.5)**
		2 or 3	**96**	**(21.5)**
Haemoglobin (g/dL)			**11.5**	**(±1.7)**
Adjusted Calcium (mmmol/l)			**2.38**	**(±0.3)**
Serum Phosphate (mmmol/l)			**1.64**	**(±0.5)**
Calcium Phosphate Product (mmol^2/l^2)			**3.88**	**(±1.2)**

Table 4.1 Clinical, blood and cardiac information for patients.

Data are number with percentage in parentheses or mean ± standard deviation except renal replacement time and CRP where median and interquartile range are used.

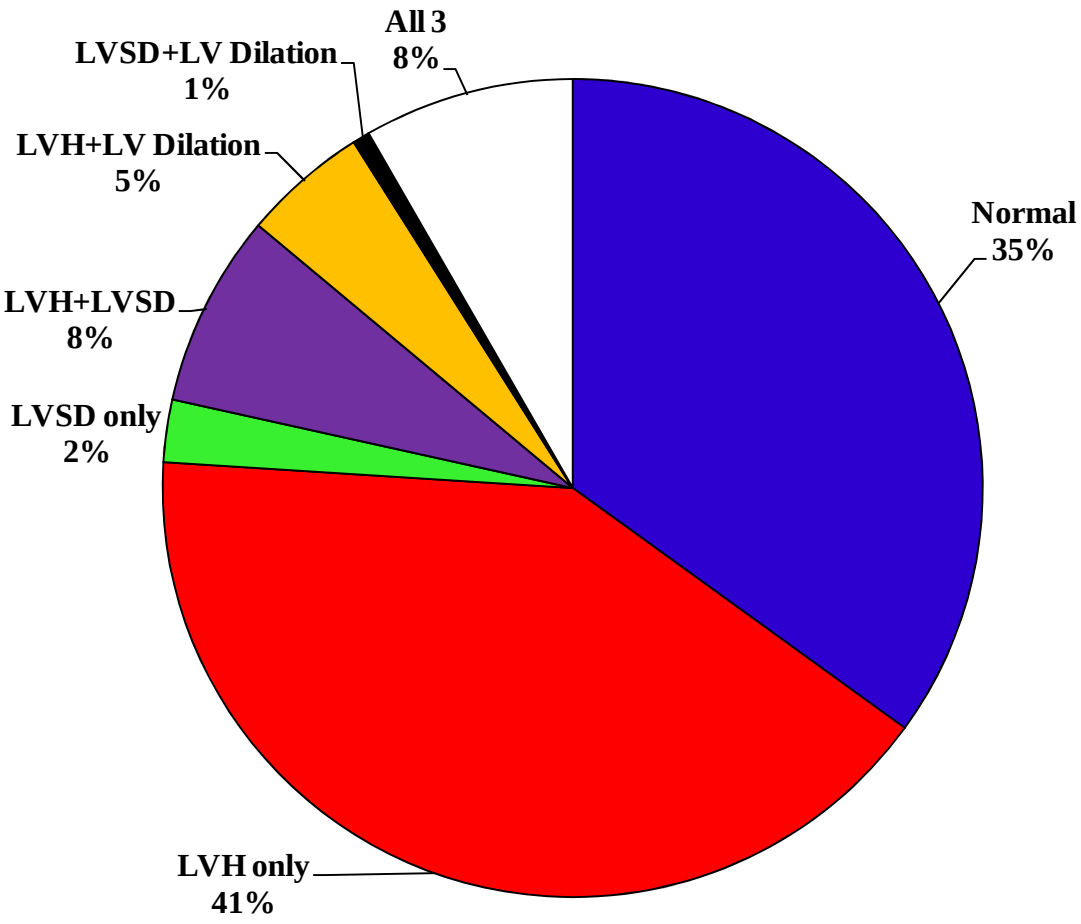


Figure 4.1 Distribution of abnormalities in patient cohort

4.3.2 Patient survival- all cause mortality

There were 95 (21.3%) deaths during the follow up period. Eighteen deaths occurred after transplantation. Figure 4.2 shows the causes of death. CV causes accounted for 53 (55.8%) deaths, with infective and malignant causes recorded for 29 (30.5%) and 5 (5.3%) respectively. The cause of death was unknown or due to other causes in 8 (8.4%) of cases.

Comparisons between patients who were alive and dead at the end of the study are shown in Table 4.2. Patients who died during the study were significantly older, and more likely to have a past medical history of diabetes mellitus, ischaemic heart disease and cerebrovascular disease. In addition, patients who died had significantly poorer LV systolic function and more likely to have LV dilatation on CMR and an abnormal screening ECG. There were fewer transplants and a lower mean diastolic blood pressure in the group that died, but this did not reach statistical significance. Patients with 2 or more abnormalities were more likely to die during follow up.

Transplant censored survival analyses were performed by removing transplant recipients from the study at the time of operation. This was performed to account for the beneficial effect of renal transplantation on outcome. Patient survival was not significantly affected by the presence of LVH on CMR (Figure 4.3a). However, presence of LVSD and LV dilatation were significantly associated with reduced mean patient survival (Figure 4.3b and 4.3c respectively). Furthermore, presence of 2 or more cardiac abnormalities was significantly associated with poorer survival compared to patients with normal hearts or 1 abnormality (figure 4.3d). Survival was

poorer in patients with 3 abnormalities compared to 2 (mean survival times 2 abnormalities 6.4±2.0y vs. 3 abnormalities 4.8±3.1y; p=0.01, graph not shown).

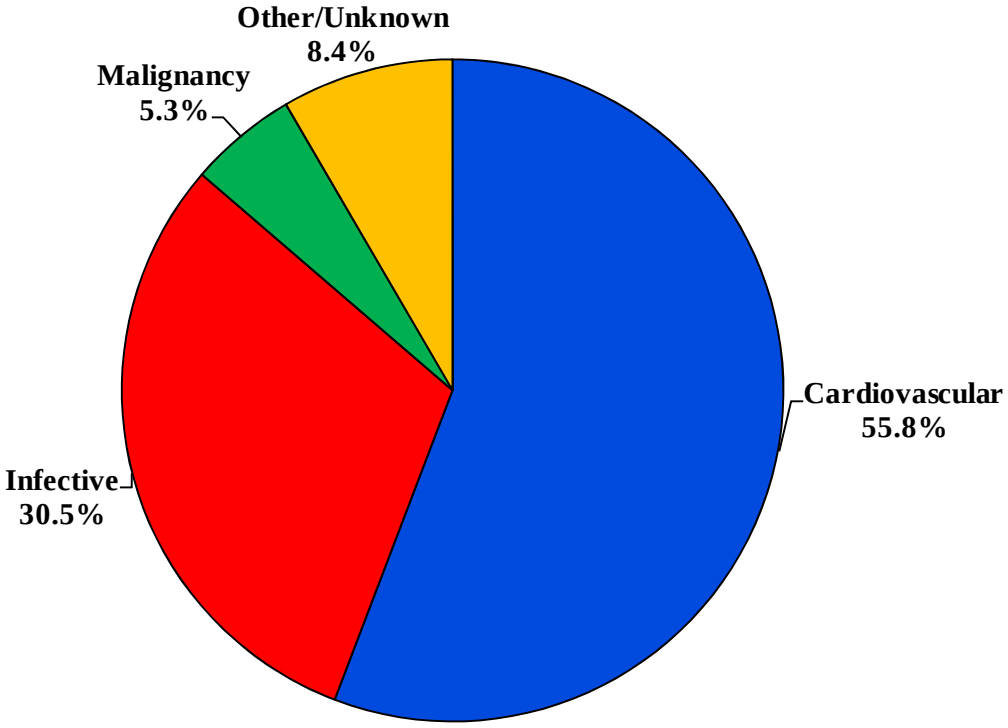


Figure 4.2 Pie Chart showing causes of death. Cardiovascular death is the commonest cause of death in this cohort.

Variable			Alive N=351	Dead N=95	p
Transplants			96 (27.4)	18 (18.9)	0.09
Age (years)			52.1 (±11.9)	56.3 (±10.8)	<0.01
Male (%)			238 (67.7)	59(62.1)	0.30
BMI (kg/m^2)			26.1 (±4.9)	25.7 (±4.7)	0.25
Primary Renal Diagnosis					
	Diabetic Nephropathy		73 (20.8)	25 (26.3)	0.36
	ADPCKD		37 (10.5)	13 (13.7)	
	Glomerulonephritis		72 (20.5)	16 (16.8)	
	Pyelonephritis		37 (10.5)	4 (4.2)	
	Renovascular disease		23 (6.6)	6 (6.3)	
	Unknown/Other		109 (31.1)	31 (32.6)	
Systolic BP (mmHg)			141.1 (±24.8)	137.4 (24.1)	0.22
Diastolic BP (mmHg)			82.5 (13.2)	80.8 (12.6)	0.09
RRT Time (HD and PD only)			1.5 (4.3)	1.9 (4.4)	0.51
RRT	HD		190 (54.1)	49 (51.6)	
	PD		44 (12.5)	18 (18.9)	0.37
	Predialysis		107 (30.5)	27 (28.4)	
	Failing Trans.		10 (2.8)	1 (1.1)	
Diabetes mellitus			105 (29.9)	42 (44.2)	0.03
Ischaemic Heart Disease			61 (17.4)	29 (30.5)	0.01
Hypertension			321 (91.5)	91 (95.8)	0.16
Cerebrovascular disease			27 (7.7)	14 (14.7)	0.04
Peripheral vascular disease			34 (9.7)	8 (8.4)	0.71
Smoking	Never		172 (49.0)	47 (49.5)	
	Current		99 (28.2)	26 (27.4)	0.99
	Ex		80 (22.8)	22 (23.2)	
Dyslipidaemia			151 (43.0)	43 (45.3)	0.70
Abnormal ECG			108 (30.8)	43 (45.3)	<0.01
CMR	Ejection Fraction (%)		65.6(±12.5)	62.3(±15.3)	0.02
Findings	Myocardial mass/BSA		95.2 (±33.5)	97.2 (±33.1)	0.67
	EDV/BSA (ml/ m^2)		73.5 (±30.5)	78.4 (±33.5)	0.18
	ESV/BSA (ml/ m^2)		27.0(±21.2)	32.8(±28.5)	0.07
	LVSD(EF<55%)		60 (17.1)	25 (26.3)	0.04
	LVH		211 (60.1)	65 (68.4)	0.14
	LV dilatation		43 (12.3)	19 (20)	0.05
Number of abnormalities		0	127 (35.2)	29 (30.5)	
		1	155 (44.1)	39 (41.1)	0.02
		2 or 3	69(19.7)	27(28.4)	
Haemoglobin (g/dL)			11.5 (±1.7)	11.3(±1.5)	0.24
Adjusted Calcium (mmmol/l)			2.38 (±0.3)	2.37(±0.2)	0.87
Serum Phosphate (mmmol/l)			1.66 (±0.5)	1.70(±0.5)	0.61
Calcium Phosphate Product (mmol^2/l^2)			3.94 (±1.2)	1.70 (±0.5)	0.53

Table 4.2 Comparison between patients alive or dead at the end of the study.

Data are number with percentage in parentheses or mean ± standard deviation except for RRT time where median and interquartile range and shown. Tests of significance are t-test and Chi-square except RRT time where Mann-Whitney U Test is performed.

Figure 4.3a Mean survival: No LVH (n=170) 6.5 ±2.5y vs. LVH (n=276) 6.3 ±2.7y; p=0.56.

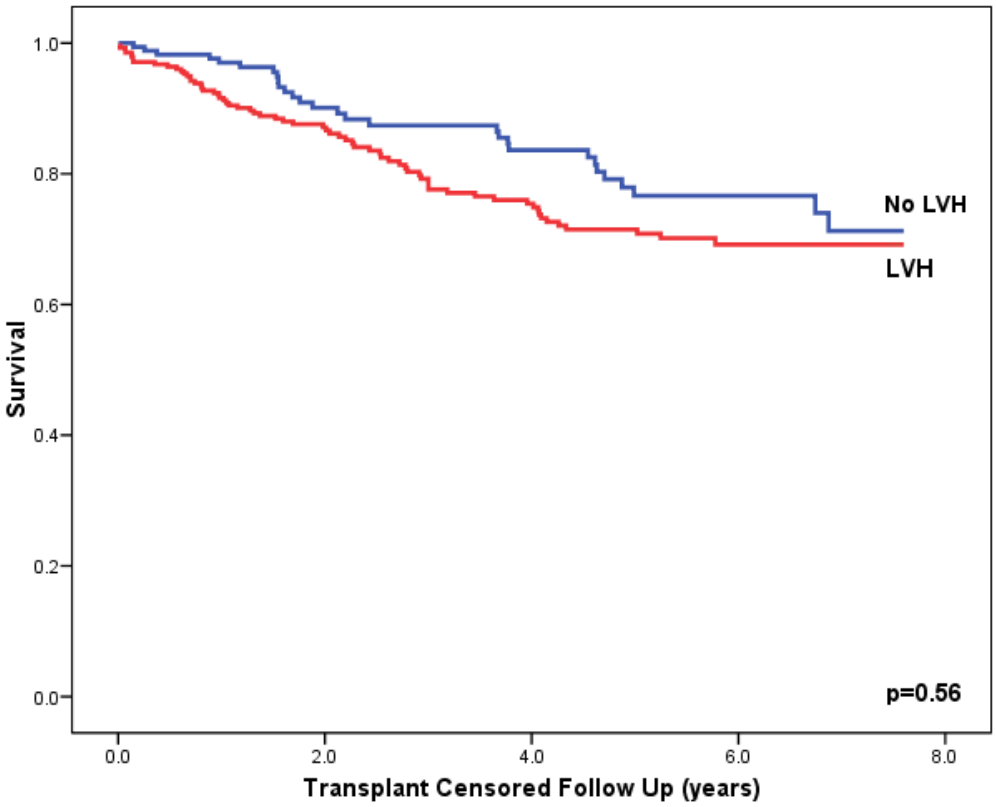


Figure demonstrating no significant difference in survival between patients with and without LVH

Figure 4.3b Mean survival: No LVSD (n=361) 6.5 ±2.5y vs. LVSD (n=85) 5.6 ±3.2y; p=0.01

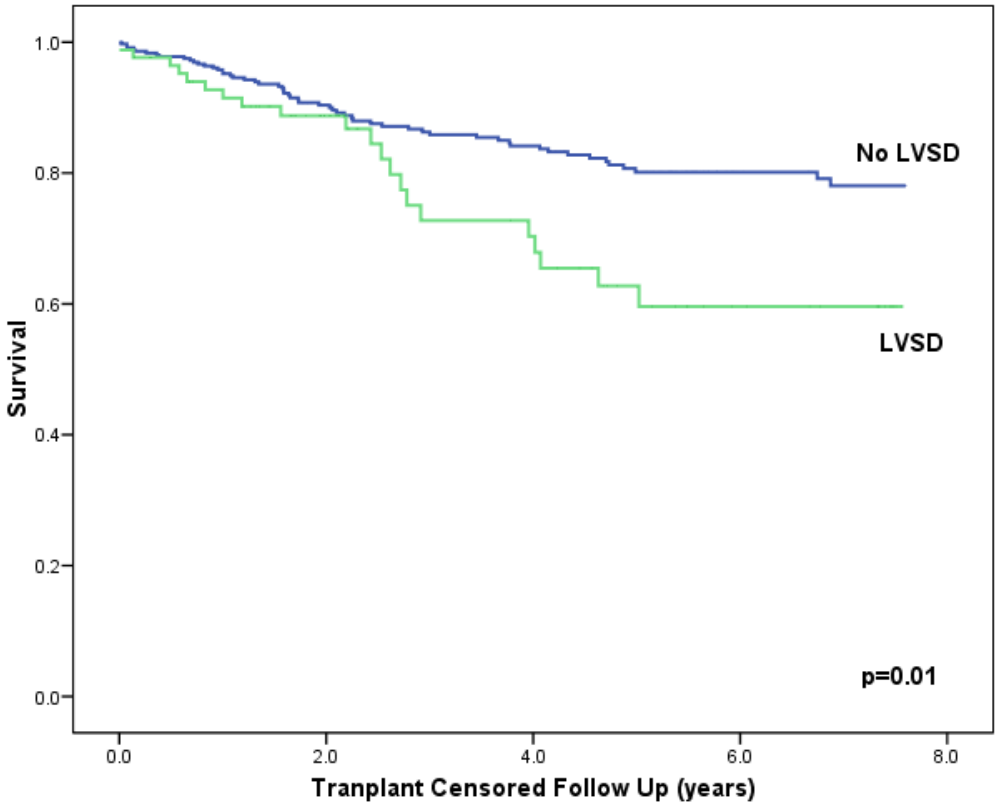


Figure demonstrating association of LVSD with reduced patient survival.

Figure 4.3c Mean survival: No LV Dilatation (n=384) 6.5 ±2.5y vs. LV Dilatation (n=62) 5.7 ±2.9y; p=0.04.

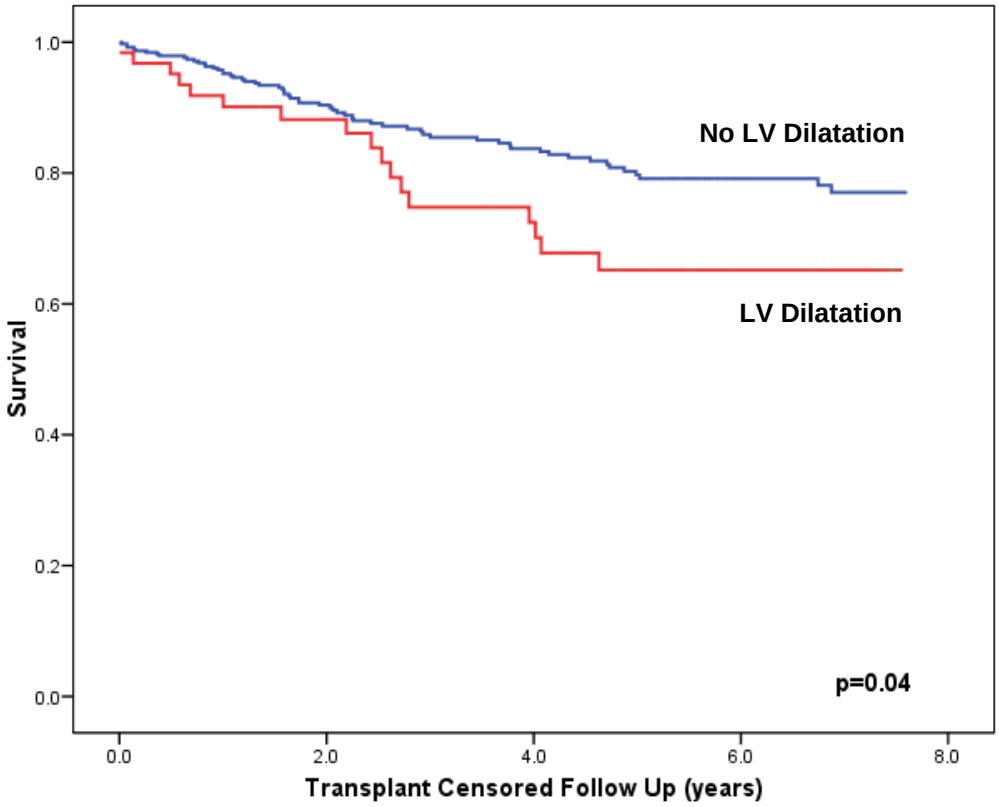


Figure demonstrating association of LV dilatation with reduced patient survival.

Figure 4.3d Mean survival for number of abnormalities: None (n=156) 6.6 ±2.2y, 1 abnormality (n=94) 6.6 ±2.5y, 2or 3 abnormalities (n==97) 5.6 ±3.0y

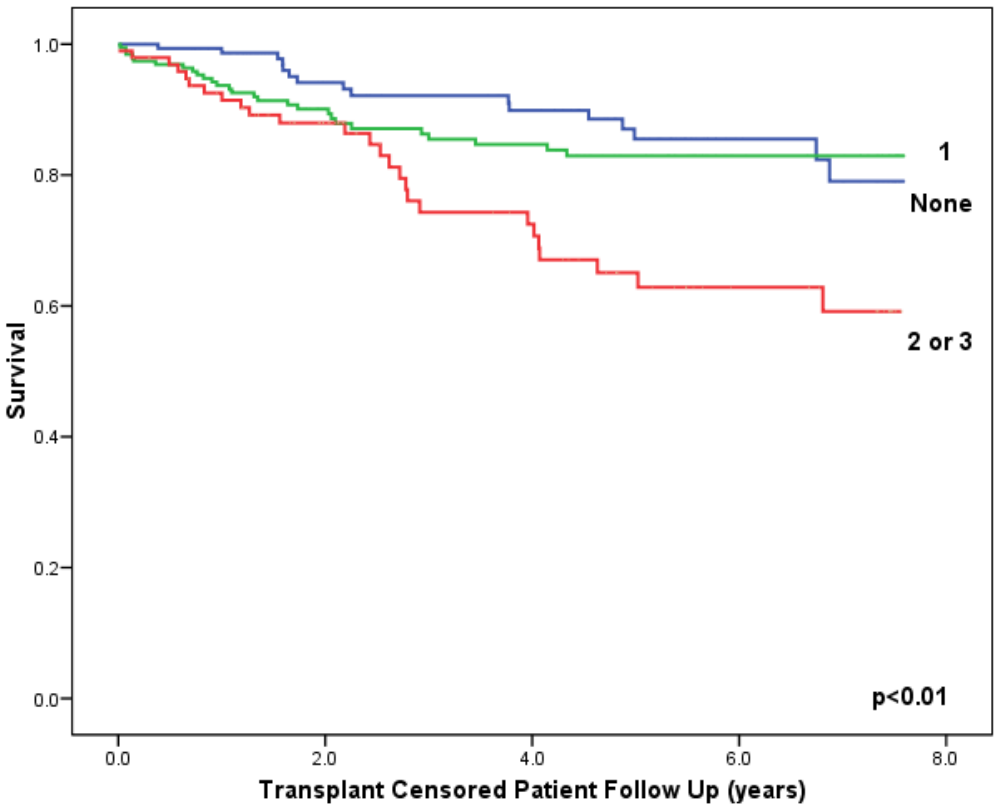


Figure demonstrating reduction in survival of patients with higher frequency of cardiac abnormalities

A Cox backward stepwise regression model was performed to indentify the most robust model for transplant censored patient survival (Table 4.3). Increasing age, past history of ischaemic heart disease and presence of LVSD on CMR were significant independent predictors of death. In Chapter 3, it was shown that combinations of myocardial abnormalities are often present. To this end, the number of abnormalities was entered into the multivariate model, as opposed to the abnormality present. Similarly, older age, clinical history of ischaemic heart disease and presence of 2 or 3 abnormalities independently predicted poorer survival.

		Univariate Analyses			Multivariate Analyses		
Variable		**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age (per year)		**1.05**	**1.02, 1.07**	**<0.01**	**1.05**	**0.97, 1.07**	**<0.01**
Ischaemic Heart Disease		**2.18**	**1.35,3.51**	**<0.01**	**1.63**	**1.07, 2.72**	**0.05**
No. of	**0**	**1.00**			**1.00**		
abnormalities	**1**	**0.75**	**0.52, 1.50**	**0.75**	**1.01**	**0.57, 1.76**	**0.88**
	2 or 3	**1.97**	**1.12,3.43**	**0.01**	**1.98**	**1.09, 3.58**	**0.02**
LVSD (EF<55%)		**2.02**	**1.23,3.32**	**<0.01**	†		
LV dilation		**1.72**	**1.01, 2.96**	**0.05**	†		
Abnormal ECG		**1.99**	**1.27,3.11**	**<0.01**			
BMI (per kg/m^2)		**0.98**	**0.94,1.02**	**0.99**			
Systolic BP (per mmHg)		**0.82**	**0.99,1.01**	**0.82**			
Diastolic BP (per mmHg)		**0.99**	**0.97,1.01**	**0.10**			
RRT Time (per year)		**1.03**	**0.91,1.18**	**0.62**			
RRT	**HD**	**1.00**					
	PD	**1.83**	**1.02,3.30**	**0.06**			
	Predialysis	**1.17**	**0.67,1.97**	**0.55**			
	Failing Trans.	**0.46**	**0.06,3.36**	**0.44**			
Diabetes mellitus		**1.29**	**0.78,2.10**	**0.30**			
Hypertension		**1.27**	**0.47,3.50**	**0.64**			
Cerebrovascular disease		**1.72**	**0.80,3.67**	**0.16**			
Peripheral vascular disease		**0.75**	**0.29,1.92**	**0.55**			
Smoking	**Never (ref)**	**1.00**					
	Current	**1.05**	**0.60,1.83**	**0.86**			
	Ex	**0.93**	**0.48,1.77**	**0.82**			
Dyslipidaemia		**1.33**	**0.88,2.09**	**0.21**			
Ejection fraction (per %)		**0.98**	**0.96, 1.03**	**0.87**			
LVMI (per g/m^2)		**1.00**	**0.98,1.01**	**0.40**			
EDV/BSA (per ml/ m^2)		**0.99**	**0.99, 1.06**	**0.27**			
ESV/BSA (per ml/ m^2)		**1.03**	**0.99,1.05**	**0.12**			
LVH		**1.23**	**0.79, 2.05**	**0.32**			
Haemoglobin (per g/dL)		**0.94**	**0.78, 1.14**	**0.56**			
Adjusted Calcium (per mmmol/l)		**1.04**	**0.01, 4.50**	**0.99**			
Serum Phosphate (per mmmol/l)		**0.87**	**0.01, 7.04**	**0.89**			
CaPO4 Product (per mmol^2/l^2)		**1.04**	**0.40, 12.6**	**0.96**			

† Multivariate model when number of abnormalities replaced by LVSD and LV Dilatation

Variable	HR	95% CI	p
Age (per year)	**1.05**	**1.13,3.27**	**<0.01**
Ischaemic Heart Disease	**1.59**	**0.95,2.69**	**0.07**
LVSD (EF<55%)	**2.10**	**1.23,3.43**	**<0.01**
LV dilatation			**NS**

Table 4.3 Results of univariate and multivariate Cox regression survival analyses of all patients screened; all-cause mortality is the dependable variable
Hazard ratios (95% confidence intervals) are shown. Alternative model with individual LV abnormalities entered is also shown.

4.3.3 Patient Survival- cardiovascular mortality

Similar survival analyses were performed to better define variables associated with transplant censored CV mortality only. There were 53 CV deaths during the follow up period. Six of these deaths occurred after renal transplantation and thus were censored at the time of transplantation.

Table 4.4 shows comparison of patients who experienced CV death compared to those who died due to other causes or were alive at the end of the study. As before, CV death was significantly more common in older patients and those with a history of ischaemic heart disease and diabetes mellitus. In addition, patients who died from CV causes were more likely to have an abnormal screening ECG, and were more likely to demonstrate poorer LV function, LVH and LV dilatation on CMR. CV death was significantly associated with 2 or more cardiac abnormalities. There were no significant differences in the presence of other CV risk factors assessed (hypertension, cerebrovascular and peripheral vascular disease, dyslipidaemia and smoking history).

Transplant censored survival analyses demonstrated significantly poorer CV survival when LVH, LVSD and LV dilatation were present on CMR at the time of recruitment into the study (Figure 4.4 a, b, c respectively). Similarly, survival was significantly reduced when 2 or all 3 abnormalities were present. Presence of a single abnormality did not significantly affect CV death (Figure 4.4d). CV survival was poorer in patients with 3 abnormalities compared to 2 but this did not reach statistical significance (mean survival times 2 abnormalities 6.8±2.1y vs. 3 abnormalities 5.8±2.8y; p=0.07, graph not shown).

Variable			Alive/Non CV Death N=393	CV Death N=53	p
Transplants			**106 (27.0)**	**8 (15.1)**	**0.06**
Age (years)			**52.5 (±11.9)**	**56.6 (±10.2)**	**0.02**
Male (%)			**256 (65.1)**	**41(77.4)**	**0.08**
BMI (kg/m^2)			**25.9 (±4.9)**	**25.9 (±4.8)**	**0.92**
Primary Renal Diagnosis					
	Diabetic Nephropathy		**84 (21.4)**	**14 (26.4)**	**0.12**
	ADPCKD		**43 (10.9)**	**7 (13.2)**	
	Glomerulonephritis		**77 (19.6)**	**11 (20.8)**	
	Pyelonephritis		**41 (10.4)**	**0**	
	Renovascular disease		**26 (6.6)**	**3 (5.7)**	
	Unknown/Other		**122 (31.0)**	**18 (34.0)**	
Systolic BP (mmHg)			**140.8(±24.7)**	**137.0 (±24.3)**	**0.32**
Diastolic BP (mmHg)			**82.1(±13.1)**	**79.6(±13.7)**	**0.21**
RRT Time (HD and PD only)			**1.6(4.3)**	**1.4(4.5)**	**0.51**
RRT	**HD**		**211 (53.7)**	**38 (52.8)**	
	PD		**53 (13.5)**	**9 (17.0)**	**0.59**
	Predialysis		**118 (30.0)**	**16 (32.0)**	
	Failing Trans.		**11 (2.8)**	**0**	
Diabetes mellitus			**117 (29.8)**	**30 (56.6)**	**0.04**
Ischaemic Heart Disease			**70 (17.8)**	**20 (37.7)**	**<0.01**
Hypertension			**361 (91.9)**	**51 (96.2)**	**0.26**
Cerebrovascular disease			**35 (8.9)**	**6 (11.3)**	**0.57**
Peripheral vascular disease			**36 (9.2)**	**6 (11.3)**	**0.61**
Smoking	**Never**		**194 (49.4)**	**25 (47.2)**	**0.58**
	Current		**112 (28.5)**	**13 (24.5)**	
	Ex		**87 (22.1)**	**15 (28.3)**	
Dyslipidaemia			**169 (43.0)**	**25 (47.2)**	**0.57**
Abnormal ECG			**124 (31.6)**	**27 (50.9)**	**<0.01**
Ejection Fraction (%)			**65.7 (±12.6)**	**58.7 (±16.4)**	**<0.01**
Myocardial mass/BSA			**95.3(±33.2)**	**101.5 (±4.7)**	**0.20**
EDV/BSA (ml/ m^2)			**73.4 (±30.4)**	**83.0(±32.7)**	**0.04**
ESV/BSA (ml/ m^2)			**26.9 (±21.1)**	**38.3 (±32.7)**	**0.02**
LVSD (EF<55%)			**69 (17.6)**	**16 (30.2)**	**<0.01**
LVH			**236 (60.1)**	**40(75.5)**	**<0.01**
LV dilatation			**48 (12.2)**	**14 (26.4)**	**<0.01**
Number of abnormalities		**0**	**144 (36.6)**	**12 (22.6)**	**<0.01**
		1	**171 (43.5)**	**23 (43.4)**	
		2 or 3	**78 (19.8)**	**18 (33.9)**	
Haemoglobin (g/dL)			**11.5 (±1.7)**	**11.3(±1.6)**	**0.33**
Adjusted Calcium (mmmol/l)			**2.37 (±0.2)**	**2.37 (±0.2)**	**0.78**
Serum Phosphate (mmmol/l)			**1.67 (±0.5)**	**1.65 (±0.4)**	**0.80**
Calcium Phosphate Product (mmol^2/l^2)			**3.97 (±1.2)**	**3.93(±1.1)**	**0.88**

Table 4.4 Comparison between patients who experienced CV death and those who did not at the end of the study.

Data are number with percentage in parentheses or mean ± standard deviation except for RRT time where median and interquartile range and shown.

Figure 4.4a Mean survival: No LVH 7.2±1.3y vs. LVH 6.8±2.1y; p=0.05.

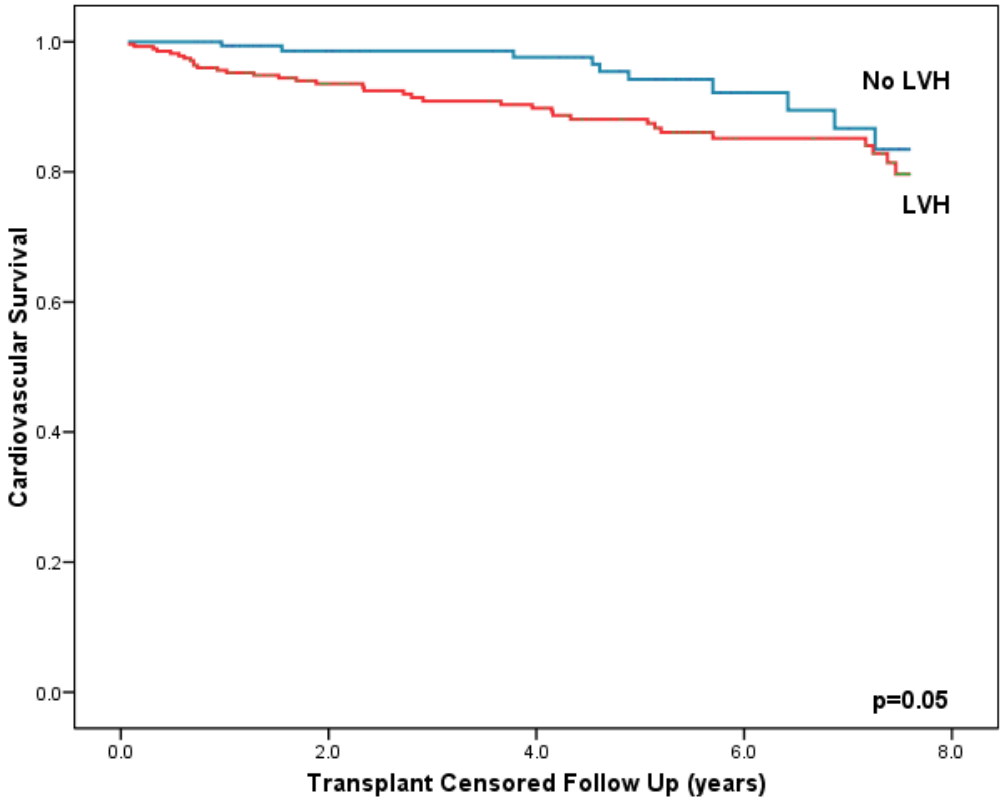


Figure demonstrating reduction in CV survival of patients with LVH

Figure 4.4b Mean survival: No LVSD 7.2 ±1.3y vs. LVSD 6.1±2.8y; p<0.001

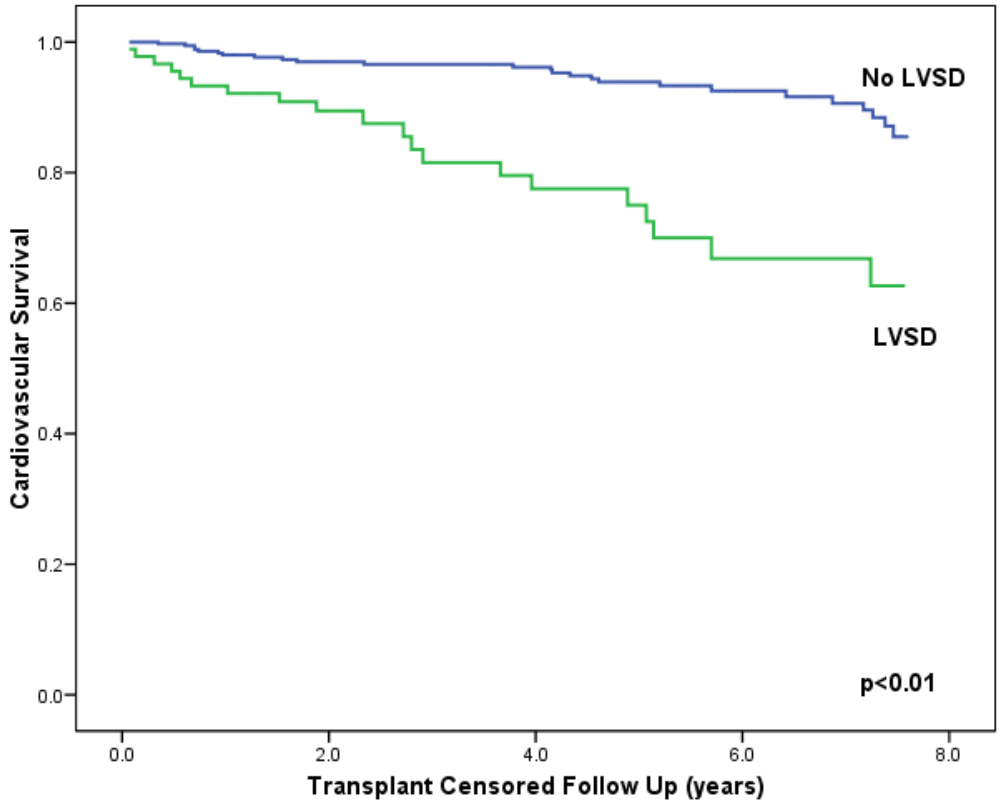


Figure demonstrating reduction in CV survival of patients with LVSD

Figure 4.4c Mean survival: No LV Dilatation 7.1±1.6y vs. LV Dilatation 6.2±2.6y; p=0.003

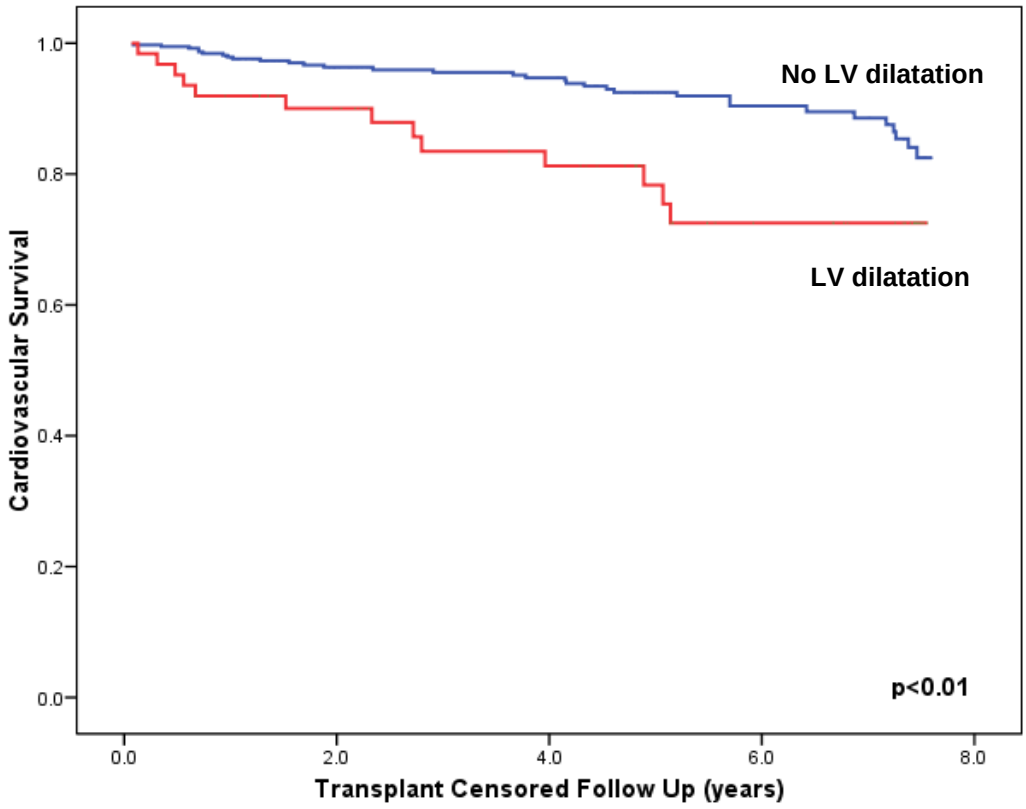


Figure demonstrating reduction in CV survival of patients with LV dilatation

Figure 4.4d Mean survival for number of abnormalities: None= 7.3±1.3y, 1 abnormality = 7.1±1.7y, 2 or 3 abnormalities= 6.4±2.5y; p=0.002.

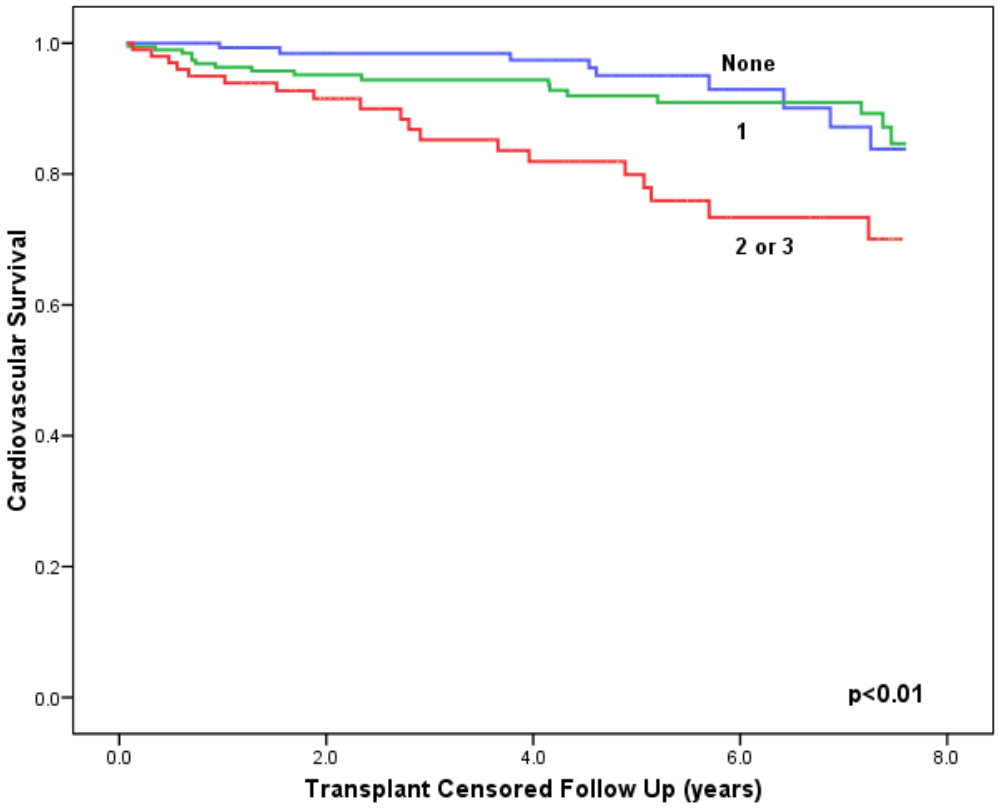


Figure demonstrating reduction in CV survival of patients with higher frequency of cardiac abnormalities

As before, a Cox backward stepwise regression model was performed to identify factors associated with transplant censored CV survival (Table 4.4). Increasing age, past history of ischaemic heart disease and presence of LV dilatation on CMR were significant independent predictors of CV death. When entering number of abnormalities into the multivariate model, older age and presence of 2 or 3 abnormalities independently predicted CV death.

		Univariate Analyses			Multivariate Analyses		
Variable		**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age (per year)		**1.05**	**1.02,1.08**	**<0.01**	**1.06**	**1.03,1.09**	**<0.01**
No. of	**0**	**1.00**			**1.00**		
abnormalities	**1**	**1.43**	**0.64,3.18**	**0.387**	**1.46**	**0.65, 3.26**	**0.36**
	2 or 3	**3.39**	**1.53,7.51**	**<0.01**	**3.80**	**1.71, 8.41**	**<0.01**
Ischaemic Heart Disease		**2.18**	**1.19,3.99**	**0.01**			
LVSD (EF<55%)		**2.77**	**1.51,5.10**	**<0.01**	**		
LV dilatation		**2.51**	**1.32,4.78**	**<0.01**	**		
Ejection Fraction (per %)		**0.96**	**0.95, 0.98**	**<0.01**			
Abnormal ECG		**2.00**	**1.12,3.56**	**0.02**			
ESV/BSA (per ml/ m^2)		**1.04**	**1.01, 1.06**	**<0.01**			
LVH		**2.00**	**0.99,4.03**	**0.05**			
BMI (per kg/m^2)		**1.02**	**0.96, 1.08**	**0.53**			
Systolic BP (per mmHg)		**1.00**	**0.98, 1.02**	**0.72**			
Diastolic BP (per mmHg)		**0.99**	**0.96, 1.02**	**0.57**			
RRT Time (per year)		**0.99**	**0.92,1.05**	**0.66**			
RRT	**HD**	**1.00**					
	PD	**1.26**	**0.57, 2.81**	**0.56**			
	Predialysis	**1.07**	**0.55, 2.09**	**0.85**			
	Failing Trans.	**0.98**	**0.46, 2.07**	**0.97**			
Diabetes mellitus		**0.94**	**0.52, 1.71**	**0.84**			
Hypertension		**1.39**	**0.34, 5.76**	**0.65**			
Cerebrovascular disease		**1.36**	**0.54, 3.45**	**0.51**			
Peripheral vascular disease		**1.70**	**0.67, 4.31**	**0.27**			
Smoking	**Never (ref)**	**1.00**					
	Current	**1.06**	**0.53, 2.15**	**0.87**			
	Ex	**1.07**	**0.53, 2.16**	**0.86**			
Dyslipidaemia		**1.40**	**0.78, 2.51**	**0.26**			
LVMI (per g/m^2)		**1.01**	**0.97, 1.02**	**0.34**			
EDV/BSA (per ml/ m^2)		**1.98**	**0.96, 2.08**	**0.71**			
LV dilatation							
Haemoglobin (per g/dL)		**0.77**	**0.56, 1.07**	**0.11**			
Adjusted Calcium (per mmmol/l)		**0.45**	**0.08, 2.67**	**0.38**			
Serum Phosphate (per mmmol/l)		**0.69**	**0.30,1.59**	**0.38**			
CaPO4 Product (per $mmol^2/l^2$)		**0.89**	**0.62, 1.27**	**0.51**			

** **Multivariate model when number of abnormalities replaced by LVSD and LV Dilatation**

Variable	HR	95% CI	p
Age (per year)	**1.05**	**1.02, 1.08**	**0.001**
Ischaemic Heart Disease	**1.89**	**1.01, 3.46**	**0.04**
LVSD (EF<55%)			**NS**
LV dilatation	**2.46**	**1.27, 4.78**	**0.008**

Table 4.4 Results of univariate and multivariate Cox regression survival analyses of all patients screened; CV mortality is the dependable variable.

Hazard ratios (95% confidence intervals) are shown. Alternative model with individual LV abnormalities (**) entered are also shown

4.5 DISCUSSION

The determinants of uraemic cardiomyopathy were described in Chapter 3. The development of LV abnormalities was described as a process initiated and perpetuated by elevated cardiac preload and afterload which are very common in ESRD patients due to fluid overload, vascular calcification and systemic hypertension. Furthermore, due to these persistent cardiac stressors it was very common for ESRD patients to have more than one LV abnormality presumably representing different stages in the patho-physiological process. The rationale of therapeutic intervention would be to disrupt this process thus halting and/or reversing abnormalities and improving CV outcome in ESRD patients.

The aim of this study was to investigate the effect of myocardial abnormalities detected by CMR on CV survival in ESRD patients. Although, similar studies have demonstrated reduced survival in ESRD patients with LVH, LVSD and LV dilatation detected by echocardiography, no such long term outcome data are available for measurements recorded by CMR.

4.5.1 Uraemic cardiomyopathy and outcome

Examining the cohort as a whole, there were only 95 deaths (21.3%) deaths over a median follow up time of 4.0 (IQR 4.2) years. This mortality rate was lower compared to other studies investigating outcome in all ESRD patients where rates between 30-50% have been observed over a similar follow up time. However, the patients of this cohort were referred for CV assessment as part of their preparation for renal transplantation and thus were deemed fit enough by their referring nephrologist to undergo renal transplantation. Other studies in the pre-transplant group have demonstrated similar rates of death on follow up (203). As in other studies, transplant censored survival was assessed for all cause and CV mortality to remove the beneficial bias conferred by renal transplantation from the analyses (134;167).

4.5.2 LVH and outcome

These data demonstrate that presence of LVH and elevated LVMI were not significantly associated with higher all cause mortality. In addition, presence of LVH was not associated with reduced survival times and did not independently predict all cause mortality on Cox proportional survival analyses. Although, presence of LVH was significantly associated with a higher CV mortality and significant reduction in CV survival, multivariate Cox survival analyses did not demonstrate LVH as independent predictors of CV death.

This result was unexpected given previous published data demonstrating elevated LV mass and presence of LVH as significant predictors of all cause and CV

mortality in ESRD patients (47;48). There are a number of reasons for these discrepancies of results.

Previous studies have used M Mode echocardiography to assess LV mass and chamber size. LVH has been reported to be present in 50-80% of patients with ESRD. The methodological inconsistencies of echocardiography, particularly at higher LVMI (>120g/m^2) have been highlighted previously. Parfrey et al (47) performed a large prospective trial in 432 patients initiating dialysis therapy and their echocardiography results compared to these data are shown in Table 4.5.

	Parfrey et al (%) Echocardiography	**These Data (%) CMR**
Normal	16	35
LVH	41 (concentric)	61.9
LVSD	15	19
LV Dilatation	28 (preserved LV function)	13.9 7.6% with preserved LV function

Table 4.5 Comparison between Parfrey et al and these data.

These differences highlight the importance of hydration status on timing of cardiac scanning. When echocardiography is used, identification of chamber borders can be inaccurate especially in fluid overloaded patients, and errors in calculation of chamber size and LV mass magnified due to the computations performed. As a result, there is a greater likelihood for patients to be incorrectly classified as having LVH (when LV mass is overestimated) or LV dilatation (when end diastolic chamber size is overestimated). CMR data presented here demonstrate a much larger proportion of patients with normal cardiac structure and fewer patients with LV

dilatation compared to echocardiography data. It should be noted that no formal distinction between eccentric and concentric LVH was made.

Serial echocardiography has provided some insight into the effect of worsening cardiac changes and patient outcome. Paoletti et al demonstrated that progression of LVH is a much stronger predictor of sudden cardiac death than the absolute value of LVMI at inception echocardiogram (89). It is most likely that these studies included ESRD subjects with chronic fluid overload and in the future, repeat CMR of patients in this cohort may help to support this hypothesis.

In summary, although presence of LVH has a statistically significant effect on CV survival in this study, it did not have as great an effect as has previously been demonstrated in echocardiography studies.

4.5.3 LVSD and outcome

From previous late gadolinium enhanced CMR studies of ESRD patients, LVSD has been significantly associated with (usually silent) ischaemic heart disease. As described in Chapter 3, micro- and macrovascular coronary disease, which are very common in ESRD patients, are significant causes of myocardial ischaemia and subsequent LVSD.

These data confirm previous echocardiography studies demonstrating a significantly poorer survival (all cause and cardiovascular) in patients with impaired LV function. The determinants of LVSD have previously been described in Chapter 3. Interestingly presence of LVSD was a significant predictor of all cause, but not

cardiovascular, mortality independent of a past clinical history of ischaemic heart disease (Tables 4.3 and 4.4) and is most likely due to:

- Presence of LVSD also being associated with higher risk of non cardiac causes of death. This has been demonstrated before (188;204), and is due to the close association of LVSD with other co-morbidities including peripheral and cerebrovascular disease and diabetes mellitus in the absence of clinically apparent ischaemic heart disease (139).
- A close association between clinical history of ischaemic heart disease and LVSD in patients who died from CV causes thus removing independent associations on multivariate Cox survival modelling.

Nonetheless, these data demonstrate a significantly poorer survival, including CV survival, in patients with LVSD on CMR.

4.5.4 LV dilatation and outcome

From these data, presence of LV dilatation was associated with significantly reduced all cause and CV survival. Presence of LV dilatation also independently predicted CV death adjusted for age and past history of ischaemic heart disease. As has been discussed previously in this thesis, LV dilatation is independently associated with LVSD and chronic fluid overload (represented by elevated mean doses of ultrafiltration in haemodialysis patients) in the absence of an adequate compensatory increase in LV mass. LV dilatation has previously been independently associated with poorer prognosis in ESRD patients (134). In particular, in patients with established LV dilatation and preserved systolic function, survival has been shown to be worse in patients with higher LV cavity volumes and inadequate compensatory

increase in LV mass. Moreover, isolated LV dilatation was not recorded in any patients from this cohort, and it is likely that LV dilatation is a marker of significant global LV disease thus explaining poor CV outcome in patients who develop this abnormality.

4.5.5 Accumulation of myocardial abnormalities and outcome

Unsurprisingly, patients who had two or more cardiac abnormalities had poorer all cause and CV survival. In addition, number of cardiac features independently predicted all cause and CV mortality in ESRD patients. The presence and number of cardiac abnormalities were not entered simultaneously into the Cox survival model due to their close association. Survival (from all and CV causes) was also worst in patients with all 3 abnormalities compared to those with a combination of two (LVH and LVSD, LVH and LV dilatation or LVSD and LV dilatation).

Presence of one abnormality did not have a significant effect on Kaplan Meier or Cox multivariate survival analyses. LVH accounted for 94% of patients with one abnormality and this reflects our earlier finding that LVH did not have as significant an influence on survival of ESRD patients as previously demonstrated. It would be interesting in the future to repeat this analysis using more patients with isolated LVSD.

4.5.6 Potential targets for intervention

The main aim of this study was to determine whether features of uraemic cardiomyopathy measured by CMR had an effect on patient CV outcome. In addition, by identifying poor prognostic features it allows targeting of potential therapeutic interventions.

As discussed in Chapter 3, it is likely that the development of cardiac abnormalities is progressive and accounts for the common finding of more than one abnormality in ESRD patients. Thus to reverse these abnormalities and improve CV prognosis, interventions should be aimed at reducing cardiac preload and afterload (i.e. hypertension, fluid overload, vascular calcification) that propel the pathophysiological process. Early studies, investigating the effect of pharmacological and dialysis interventions on myocardial structure and function have been described in Chapter 3.

Myocardial structure has been shown to change even in milder stages of CKD and continue to progress as renal function deteriorates (170; 173). Given that the prognosis in this study was not significantly different between patients with normal hearts and one abnormality, aggressively targeting patients at an early stage to prevent progression to more than one structural change may be beneficial. It is essential that measures employed to prevent development or reverse LVH, LVSD and LV dilatation in ESRD patients be employed early. Furthermore, slowing or regressing these abnormalities has not been convincingly achieved using adequately powered, randomised controlled studies and it is still not known whether

intervention will improve CV outcome. This study will hopefully provide data to power such studies in the future.

4.5.7 Limitations of current study

There were differences, particularly in mortality rates between these and previously published data. As stated previously, this is most likely due to recruitment from the pre-transplant population. However, it is likely that these results are relevant to other CKD 5 patients with more significant co-morbidities.

4.6 CONCLUSIONS

In conclusion, LVSD and LV dilatation detected by CMR are associated with higher all cause and CV mortality in ESRD patients. Although LVH significantly reduces cardiovascular survival, this is not to the extent suggested by echocardiography studies in this patient group. Although presence of one cardiac abnormality did not significantly affect survival, accumulation of two or more cardiac abnormalities was associated with a significantly poorer prognosis. These findings suggest that measures should be assessed to aggressively reverse these changes and improve cardiovascular outcome in ESRD patients.

Chapter 5

A study of determinants of mortality in ESRD patients with LVH: the role of left atrial volume.

5.1 INTRODUCTION

As previously mentioned, echocardiography studies have identified abnormalities in left ventricular structure and function, termed “uraemic cardiomyopathy”, that independently confer a poorer prognosis in ESRD patients (47).

Of these, left ventricular hypertrophy is present in approximately 67% of patients with ESRD and the most common manifestation of uraemic cardiomyopathy. Moreover, it is an independent risk factor for sudden cardiac death, heart failure, and cardiac arrhythmias in both the general population and patients receiving haemodialysis. The presence of LVH alone has a variable prognosis. Furthermore, reversal of LVH in ESRD patients has proven difficult and attempts have been made to identify additional cardiac abnormalities that predict death and are amenable to intervention (53;205;206).

The strengths of CMR over echocardiography to assess LV mass in ESRD have been described in Chapter 1. In addition, elevated left atrial (LA) volume (corrected for body surface area (BSA) or height) is an independent predictor of mortality in the general population, and in hypertensive and ESRD patients, when measured by echocardiography (207;208). Causes of increased left atrial volume (LAV) in ESRD, include mitral valve disease, fluid overload and impaired left ventricular diastolic relaxation and filling (called LV diastolic dysfunction) (209). LAV can be reliably and reproducibly measured on echocardiography and CMR using the biplane area-length method described in Chapter 2 (155;156).

The aim of this prospective study was to accurately identify a cohort of ESRD patients with LVH on CMR and to identify additional features that would confer poorer survival. Given the findings from previous studies, LAV was included in the analyses.

5.2 METHODS

5.2.1 Patients

ESRD patients were recruited from the renal transplant assessment clinic from the Western Infirmary as described in Chapter 2. Haemodialysis data, including doses of ultrafiltration, were recorded at 30 day intervals up to 180 days prior to CMR. Only patients with evidence of LVH on CMR were entered into the study. All patients were in sinus cardiac rhythm at the time of scanning.

To ensure that only non valvular causes of LA dilatation were assessed, patients with grade II to IV mitral valve regurgitation (i.e. greater than mild) on colour Doppler echocardiography were excluded from the study. Severity of mitral valve incompetence was assessed using American Heart Association/ American College of Cardiology criteria of (210):

- Colour Doppler jet area.
- Vena contracta diameter (defined as point in a fluid stream where the diameter of the stream is the least).

To obtain a large cohort of patients and achieve greater statistical power, previous CMR scans (n=46) performed by Dr Patrick Mark were added to current studies.

These scans, however, were analysed separately by the investigator (RKP) who was blinded to patients' characteristics and outcome.

5.2.2 CMR acquisition and analyses

CMR scans were acquired as part of assessment of LV mass and function and analysed as previously described. In addition, LAV was measured using the bi-plane area length method for ellipsoid bodies which was previously described in Chapter 2.

5.2.3 Mitral valve inflow Doppler velocity measurement

Echocardiography was performed by an experienced echocardiographer (Tony Cunningham, Clinical Research Iniative, Western Infirmary, Glasgow). Diastolic function was assessed using pulsed-wave Doppler (211;212) from apical four chamber views to measure the ratio of early (E) to late (A) mitral inflow peak flow velocity (E/A ratio).

5.2.4 Follow up

Patient follow up data were collected from the date of CMR scan to the 30th September 2009 from the electronic patient records of the Western Infirmary, Glasgow and Glasgow Royal Infirmary Renal units. Death from all causes was the study end point.

5.2.5 Statistical methods

Data are described as mean and standard deviation (for normally distributed data) or median (interquartile range) for non-normal data. Comparisons were made between those patients with high or low LAV by student's t test (for normal data), Mann-

Whitney U test (for non-normal data) and Chi squared test or Fisher's exact test. Survival data including survival time (mean± standard deviation) are shown as Kaplan-Meier graphs (with statistical comparison using the log rank test). These data were also analysed by Cox multivariate survival analysis to assess the influence of multiple clinical and cardiac variables on outcome. This study included transplant censored survival analyses. Variables identified as significantly influential on outcome by univariate analysis were entered into a backward stepwise regression model. All analyses were performed using SPSS v15.0 (SPSS Inc, Illinois, USA).

5.3 RESULTS

5.3.1 Patient demographics

From 312 ESRD patients assessed for renal transplantation with CMR, 201 patients with LVH were identified. Median follow up and transplant censored follow up were 3.62 years (IQR 1.2- 5.2 years) and 1.69 years (IQR 1.0-3.9 years) respectively. The mean age of patients was 51.6 (± 11.8) years; 72.1 % were male. Seventy one patients received a renal transplant during the period of study. Table 5.1 shows the mode of renal replacement therapy, past medical history and cardiac drug history.

5.3.2 Cardiac parameters

Examining the whole cohort (Table 5.1), the mean heart rate during MRI was 77 beats per minute (±26). Mean ejection fraction was 63.1% (±14.4), LVMI was 117.3g/m^2 (±31.1), EDV/BSA was 86.3 ml/m^2 (±31.4) and ESV/BSA was 34.1 ml/m^2 (±25.3). Fifty (24.9%) patients had LVSD and 49 (24.4%) had LV dilatation. Doppler mitral valve inflow velocity measurement showed a mean peak E wave

velocity of 0.74 cm/s (±0.2), mean peak A wave of 0.75 cm/s (±0.2) and E:A ratio of 1.04 (±0.5). Median LAV/BSA was 30.4 ml/m ^{2} (IQR 26.2, 34.1) and distribution of corrected LAV measurements is shown in Figure 5.1.

5.3.3 Left atrial volume

5.3.3 (a) Correlates

There were no significant correlations between LAV and patient age, dialysis vintage, LV ejection fraction, LVMI, EDV>BSA, mean dose of ultrafiltration during haemodialysis, or E:A ratio.

5.3.3 (b) Comparison dependent on median LAV

To further identify determinants and consequences of elevated LAV, patients were divided into high LAV (≥ median LAV/BSA; n=100) or low LAV (LAV\BSA <median; n=101) groups (Table 5.2). There was a significantly higher mortality in the high LAV group (low LAV 18 deaths vs. high LAV 36 deaths; $p<0.01$). High LAV was significantly associated with treatment with higher doses of ultrafiltration during haemodialysis. Low LAV was significantly associated with male sex. There were no significant differences in age, number of patients transplanted, BSA and type of renal replacement therapy or duration between high and low LAV groups. Furthermore, there were no significant differences in number of patients with diabetes mellitus, smoking history and cardiovascular (namely ischaemic heart disease, cerebrovascular and peripheral vascular diseases and chronic heart failure) history. On comparison of cardiac medications, there were no other significant

differences between the low and high LAV groups except for statin usage which was higher in the high LAV group.

5.3.3 (c) Predictors of LAV≥ median

To further identify predictors of elevated LAV, logistic regression analyses were performed with LAV/BSA≥ median as the outcome variable. Female sex and mean dose of ultrafiltration during haemodialysis were significant, independent predictors (R^2=0.27) of high LAV on CMR after logistic regression analyses.

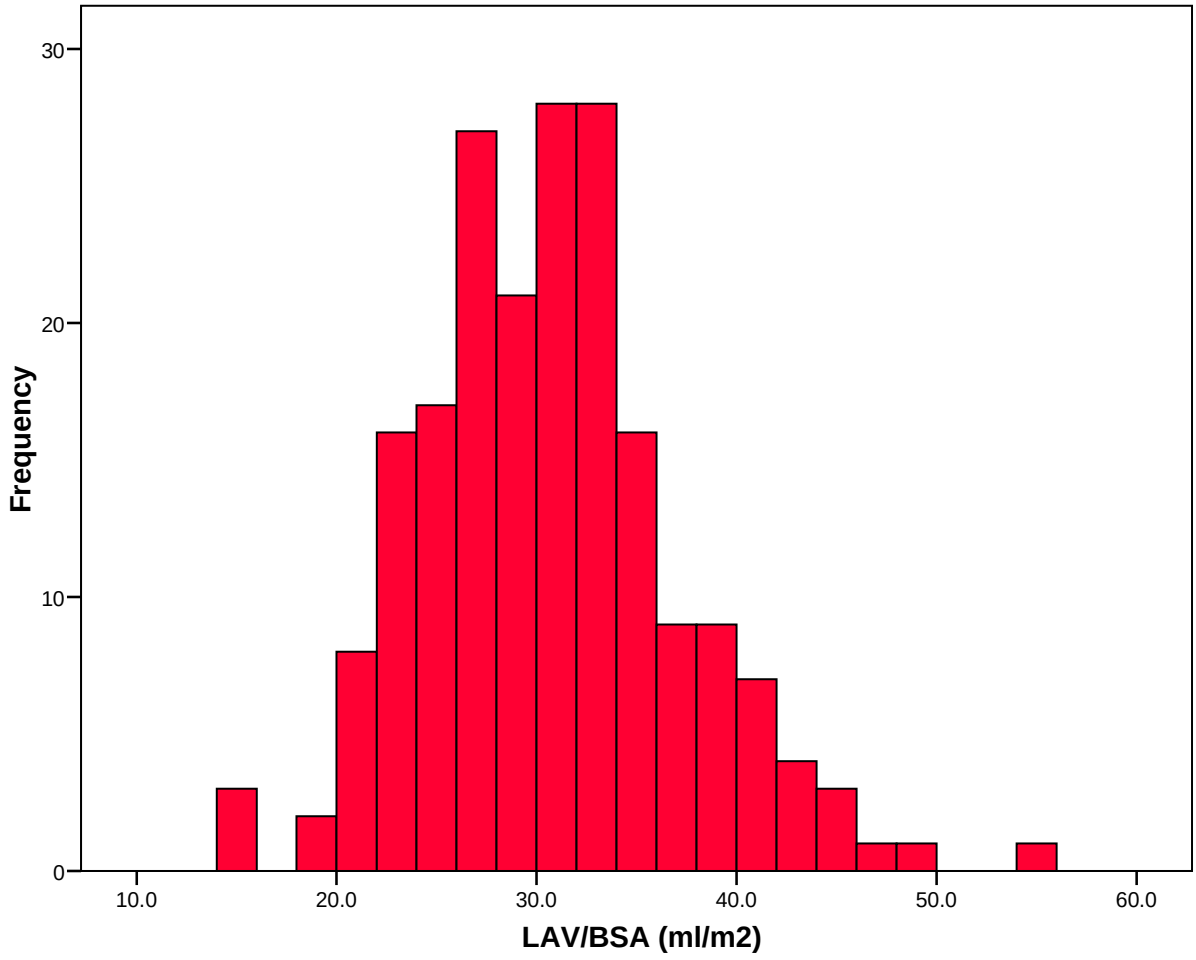


Figure 5.1 Distribution of LAV/BSA in patient cohort

Variable		Total N=201	
Deaths		54	(26.9)
Transplants		71	(35.3)
Age (years)		51.6	(±11.8)
Male (%)		145	(72.1)
Body Surface Area (m^2)		1.76	(±0.2)
Left Atrial volume (ml)		56.3	(±9.7)
Systolic BP (mmHg)		136.9	(±24.6)
Diastolic BP (mmHg)		80.9	(±12.9)
RRT	Haemodialysis	108	(53.7)
	Peritoneal dialysis	52	(25.9)
	Predialysis	41	(20.4)
Mean Ultrafiltration (HD only)		2.3	(±0.9)
Diabetes mellitus		121	(60.2)
Ischaemic Heart Disease		54	(26.9)
Heart failure		12	(6.0)
Cerebrovascular disease		12	(6.0)
Peripheral vascular disease		16	(8.0)
Smoking	Never	107	(53.2)
	Current	54	(26.9)
	Ex	40	(19.9)
Epo receptor Agonist		151	(75.1)
β Adrenoceptor Blocker		87	(43.3)
Aspirin		83	(41.3)
Warfarin		7	(3.5)
ACEI/ARB		54	(26.9)
Diuretic		60	(29.6)
Calcium Channel Blocker		58	(28.9)
α Adrenoceptor Blocker		21	(10.4)
Statin		83	(41.3)
Heart Rate		76.8	(±26.1)
Ejection Fraction (%)		63.1	(±14.4)
Myocardial mass/BSA		117.3	(±31.1)
EDV/BSA (ml/ m^2)		86.3	(±31.4)
ESV/BSA (ml/ m^2)		34.1	(±25.3)
LVSD on MRI (EF<55%)		50	(24.9)
LV dilatation		49	(24.4)
Peak E wave (cm/s)		0.74	(±0.2)
Peak A wave (cm/s)		0.75	(±0.2)
E:A ratio		1.04	(±0.4)

Table 5.1 Clinical and cardiac information for patients.

Data are number with percentage in parentheses or mean ± standard deviation.

Variable		Low LAV N=101	High LAV N=100	p
Deaths		**18(17.1)**	**36 (36)**	**<0.01**
Transplants		**40(39.6)**	**31(31)**	**0.20**
Age (years)		**50.4(±12.6)**	**52.8(±10.9)**	**0.14**
Male (%)		**82(81.2)**	**63(63)**	**<0.01**
LA volume (ml)		**50.4(±6.8)**	**62.3(±8.4)**	**<0.01**
Systolic BP (mmHg)		**135.6 (±26.2)**	**138.4 (±22.8)**	**0.51**
Diastolic BP (mmHg)		**82.2 (±13.5)**	**79.3 (±12.1)**	**0.20**
RRT	**HD**	**56(55.4)**	**52(52)**	
	PD	**23 (22.8)**	**29(29)**	**0.58**
	CKD 5	**22(21.8)**	**19(19)**	
Mean Ultrafiltration (HD only)		**2.2(±0.9)**	**2.8 (±1.2)**	**0.01**
Diabetes mellitus		**61(60.4)**	**60 (60)**	**0.95**
Ischemic Heart Disease		**24(23.8)**	**30(30)**	**0.41**
Heart failure		**6 (5.9)**	**6(6)**	**0.96**
Cerebrovascular disease		**6(5.9)**	**6(6)**	**0.96**
Peripheral vascular disease		**6(5.9)**	**10(10)**	**0.27**
Smoking	**Never**	**56(55.4)**	**51 (51)**	
	Current	**23 (22.8)**	**31 (31)**	**0.40**
	Ex	**22 (21.8)**	**18 (18)**	
Epo receptor Agonist		**72 (71.2)**	**79 (79)**	**0.10**
β Adrenoceptor Blocker		**45 (44.6)**	**42 (42)**	**0.81**
Aspirin		**38 (37.6)**	**45(45)**	**0.23**
Warfarin		**4 (4.0)**	**3 (3)**	**0.67**
ACEI/ARB		**28 (27.7)**	**26 (26)**	**0.85**
Diuretic		**31(30.7)**	**29 (29)**	**0.87**
Calcium Channel Blocker		**33 (32.7)**	**25(25)**	**0.26**
α Adrenoceptor Blocker		**13(12.9)**	**8 (8)**	**0.28**
Statin		**35 (34.7)**	**48 (48)**	**0.05**
Heart Rate		**76.3(±26.1)**	**77.4(±26.1)**	**0.31**
Ejection Fraction (%)		**63.4(±13.9)**	**62.8(±15.0)**	**0.77**
Myocardial mass/BSA		**115.7 (±29.8)**	**119.0 (±32.5)**	**0.44**
EDV/BSA (ml/ m^2)		**86.9 (±30.5)**	**85.8 (±32.4)**	**0.81**
ESV/BSA (ml/ m^2)		**33.7(±25.0)**	**34.5 (±25.7)**	**0.82**
LVSD on MRI (EF<55%)		**23 (22.8)**	**27(27)**	**0.50**
LV dilatation		**23 (22.8)**	**26(26)**	**0.59**
Peak E wave (cm/s)		**0.77 (±0.2)**	**0.71 (±0.2)**	**0.29**
Peak A wave (cm/s)		**0.76 (±0.3)**	**0.72 (±0.2)**	**0.32**
E:A ratio		**1.06 (±0.4)**	**1.02± (0.4)**	**0.72**

Table 5.2 Comparison between patients according to median LAV/BSA (low < median, high ≥ median).

Data are number with percentage in parentheses or mean ± standard deviation. Tests of significance are t-test and Chi-square.

		Univariate Analyses			Multivariate analyses		
Variable		**OR**	**95% CI**	**p**	**OR**	**95% CI**	**P**
Mean ultrafiltration(per L)		**1.64**	**1.09,2.46**	**0.02**	**1.68**	**1.09,2.57**	**0.02**
Male Sex		**0.40**	**0.21,0.75**	**0.01**	**0.35**	**0.19,0.76**	**0.04**
Age (per year)		**1.01**	**0.99, 1.04**	**0.14**			
Duration on RRT (per year)		**1.12**	**0.88, 1.42**	**0.34**			
RRT	**Predialysis**	**1.00**					
	Haemodialysis	**1.46**	**0.64, 3.32**	**0.37**			
	Peritoneal Dialysis	**1.08**	**0.52,3.32**	**0.84**			
LV ejection fraction (per %)		**0.98**	**0.98, 1.02**	**0.77**			
LVMI (per g/m^2)		**1.00**	**0.99, 1.01**	**0.44**			
EDV/BSA (per ml/m^2)		**0.99**	**0.99, 1.01**	**0.82**			
ESV/BSA (per ml/m^2)		**1.00**	**0.99,1.01**	**0.82**			
LVSD		**1.25**	**0.66, 2.38**	**0.48**			
LV Dilation		**1.19**	**0.63, 2.27**	**0.59**			
Diabetes Mellitus		**1.16**	**0.55, 2.45**	**0.70**			
Ischaemic Heart Disease		**2.49**	**0.90, 6.91**	**0.08**			
Chronic Heart Failure		**0.94**	**0.22, 5.15**	**0.94**			
Peripheral Vascular Disease		**2.19**	**0.50, 9.71**	**0.30**			
Hypercholesterolaemia		**1.66**	**0.81,3.41**	**0.17**			
Smoking	**Never**	**1.00**					
	Current	**2.24**	**0.99, 5.05**	**0.05**			
	Ex smoker	**0.99**	**0.41,2.41**	**0.99**			
Ischaemic ECG		**1.04**	**0.51,2.14**	**0.91**			
E:A ratio		**0.81**	**0.25, 2.59**	**0.72**			

Table 5.3 Simple (left) followed by backward stepwise (conditional) multiple logistic regression analyses (R^2=0.27) demonstrating independent predictors of presence LAV≥ median.

Only variables found to be significant on univariate analyses were entered into the multivariate model.

5.3.4 Survival Analyses

There were 54 (26.9%) deaths over a 6.65 year follow up period. Eleven of these deaths occurred after renal transplantation.

5.3.4 (a) Factors associated with death

Clinical and cardiac factors were compared between patients who were alive and dead at the end of the study (Table 5.4). Renal transplantation and male sex were significantly associated with lower mortality. In addition, LA volumes (corrected for BSA) were significantly higher in the group that died compared to those that survived. Similarly, LVSD on CMR and past history of ischaemic heart disease were significantly associated with a higher number of deaths. Patients who survived were more likely to have never smoked but less likely to have stopped smoking compared to those that died. When drug usage was compared, patients that died were more likely to be receiving aspirin therapy.

5.3.4 (b) Clinical indicators of outcome

The effect of left atrial and ventricular abnormalities on patient survival was investigated (Figure 5.2). Left atrial volume above the median was significantly associated with a poorer prognosis (Figure 5.2a, low LAV 5.6±2.1years vs. high LAV 4.7±2.6 years; p=0.01). Similarly, LVSD (n=50) was associated with a significant reduction in mean survival time (Figure 5.2b, no LVSD (n=151) 5.4±1.8 years vs. LVSD (n=50) 4.4±3.9years; p=0.01). Left ventricular dilatation was associated with a non-significant reduction in patient survival (Figure 5.2c, no LV dilatation (n=152) 5.2±1.9 years vs. LV dilatation (n=49) 4.7±3.7 years; p=0.18). Past history of ischaemic heart disease conferred a significant reduction in survival

(Figure 5.2d, no IHD (n=147) 5.3±2.3 years vs. IHD (n=54) 4.5±2.5years; p=0.02). Patient sex did not have a significant impact on patient survival (male 5.3±2.4 years vs. female 4.7±2.5 years; p= 0.11; graph not shown).

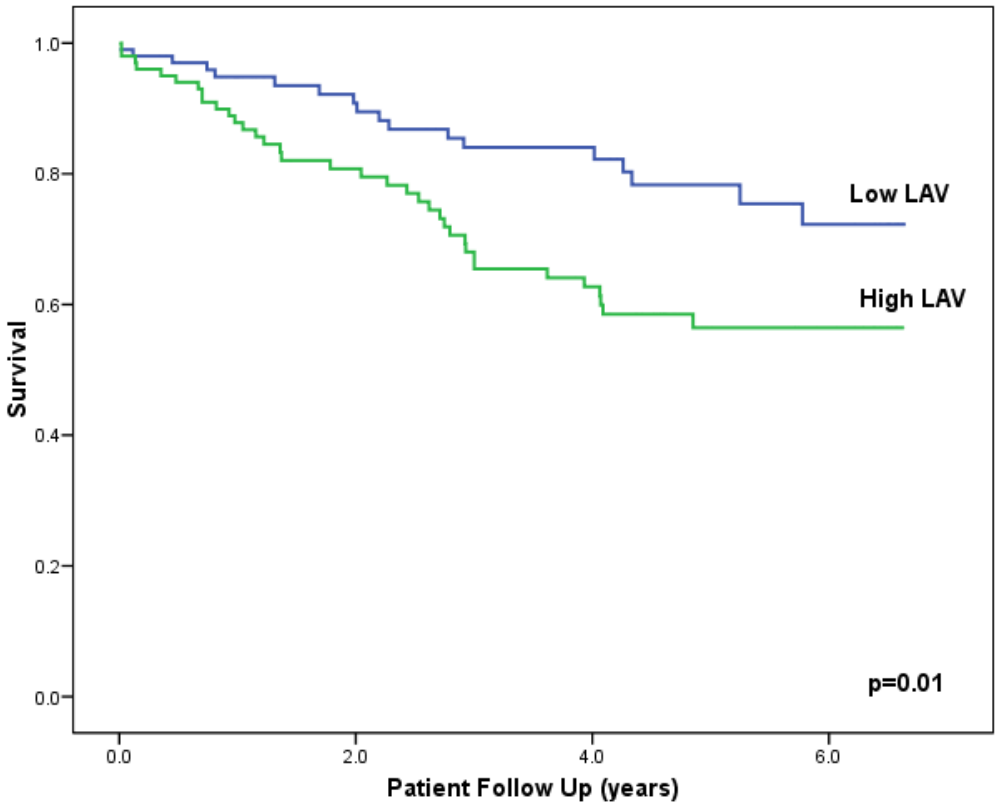
Given the survival benefits of renal transplantation, a transplant censored survival analyses was performed (Figure 5.3). As before, left atrial volume ≥median (Figure 5.3a) and LVSD (Figure 5.3b) were significantly associated with reduction in transplant censored patient survival (low LAV 5.5±2.7years vs. high LAV 4.5±2.9 years; p=0.01; no LVSD 5.3±2.7 years vs. LVSD 4.1±3.2years; p=0.02). Similarly, left ventricular dilatation was also associated with a non-significant effect on patient prognosis (Figure 5.3c, no LV dilatation 5.2±2.8 years vs. LV Dilatation 4.3±3.0 years; p=0.07). Ischaemic heart disease did not significantly affect transplant censored survival (Figure 5.3d).

Variable		Alive N=147	Dead N=54	p
Transplants		**60 (40.8)**	**11 (20.4)**	**0.01**
Age (years)		51.1(±11.4)	52.9(±12.8)	0.34
Male (%)		**112 (76.2)**	**33 (61.1)**	**0.04**
LA volume (ml/m^2)		**29.8 (16.2, 32.5)**	**33.0 (26.9,42.8)**	**<0.01**
Systolic BP (mmHg)		137.1 (±26.7)	135.6(±17.3)	0.89
Diastolic BP (mmHg)		81.0(±13.9)	80.4(±9.5)	0.79
RRT	HD	79 (53.7)	29 (53.7)	0.17
	PD	34 (23.1)	33.3 (18)	
	CKD 5	34 (23.1)	7 (13.0)	
Mean Ultrafiltration (HD only)		2.49 (±1.1)	2.6(±1.1)	0.74
Diabetes mellitus		91 (61.9)	30 (55.6)	0.42
Ischaemic Heart Disease		**32 (21.8)**	**22(40.7)**	**0.01**
Heart failure		8 (5.6)	4 (7.4)	0.74
Cerebrovascular disease		6(4.2)	6 (11.1)	0.07
Peripheral vascular disease		10 (7.0)	6 (11.1)	0.35
Smoking	**Never**	**83 (56.5)**	**24 (44.4)**	**0.04**
	Current	**41 (27.9)**	**13 (24.1)**	
	Ex	**23 (15.6)**	**17 (31.5)**	
Epo receptor Agonist		110 (77.5)	41 (80.4)	0.66
β Adrenoceptor Blocker		65 (45.8)	22 (43.1)	0.75
Aspirin		**55 (38.7)**	**28 (54.9)**	**0.05**
ACEI/ARB		39 (27.5)	15 (29.4)	0.79
Diuretic		43 (30.3)	17 (33.3)	0.69
Calcium Channel Blocker		44 (31.0)	14 (27.5)	0.64
α Adrenoceptor Blocker		14 (9.9)	7 (13.7)	0.45
Statin		58 (40.8)	25 (49.0)	0.31
Heart Rate		75.2 (±20.1)	77.1(±22.9)	0.88
Ejection Fraction (%)		63.3(±13.5)	61.6(±16.7)	0.39
Myocardial mass/BSA		117.3 (±31.3)	117.2(±16.7)	0.97
EDV/BSA (ml/ m^2)		84.2(±30.6)	92.3(±30.9)	0.11
ESV/BSA (ml/ m^2)		32.4(±22.8)	38.8(±30.8)	0.12
LVSD on MRI (EF<55%)		**32 (21.8)**	**18 (33.3)**	**0.05**
LV dilatation		32 (21.8)	17 (31.5)	0.16
Peak E wave (cm/s)		0.74 (±0.36)	0.74 (±0.2)	0.97
Peak A wave (cm/s)		0.74 (±0.2)	0.75 (±0.42)	0.97
E:A ratio		1.03 (±0.3)	1.06 (±0.4)	0.34

Figure 5.4 Comparison of patients alive and dead at the end of the study

Figure 5.2 Kaplan Meier survival curves according to (a) LAV median, (b) LVSD

(a)



(b)

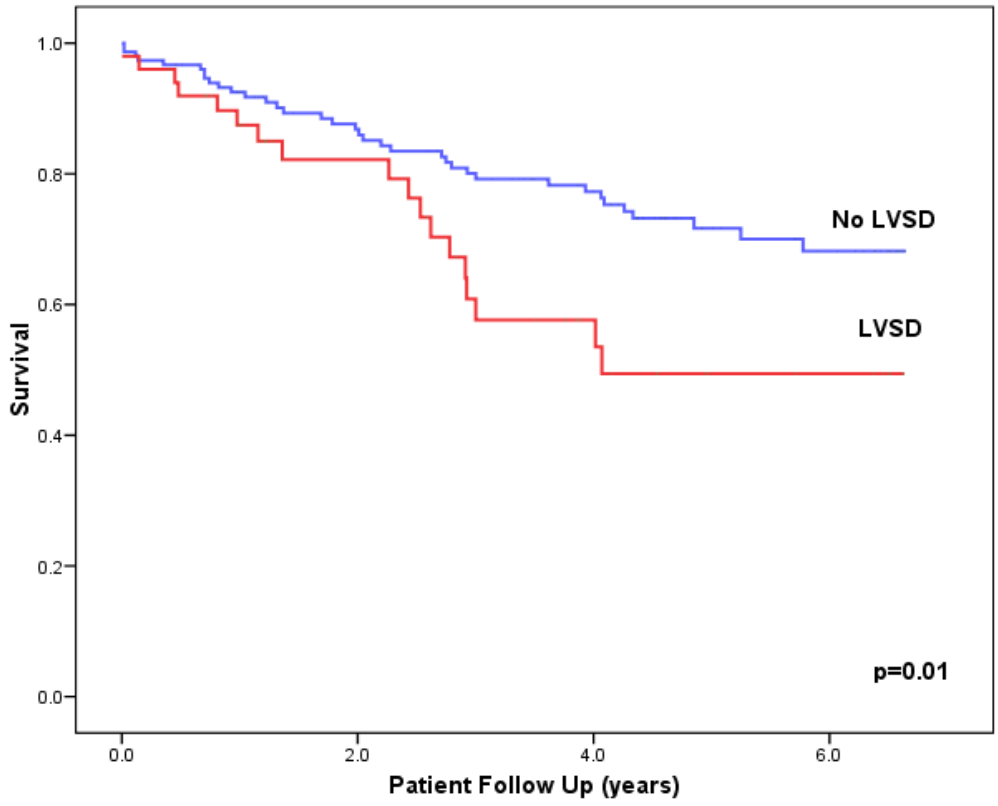
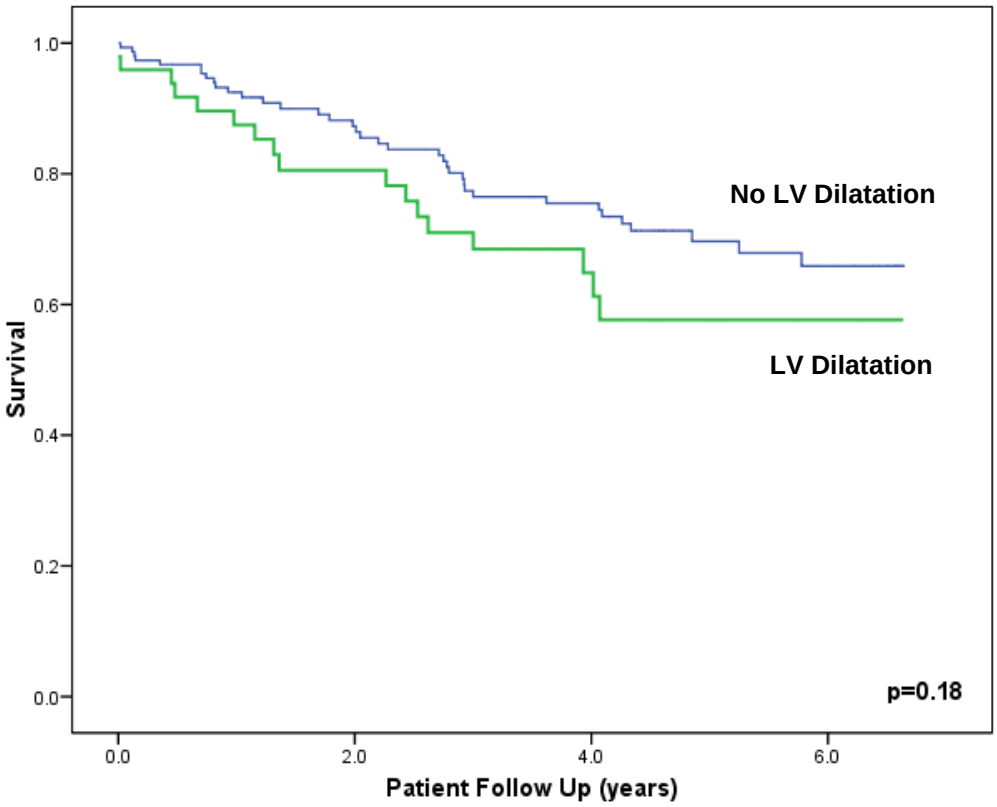


Figure 5.2 Kaplan Meier survival curves according to, (c) LV dilatation and (d) past history of ischaemic heart disease

(c)



(d)

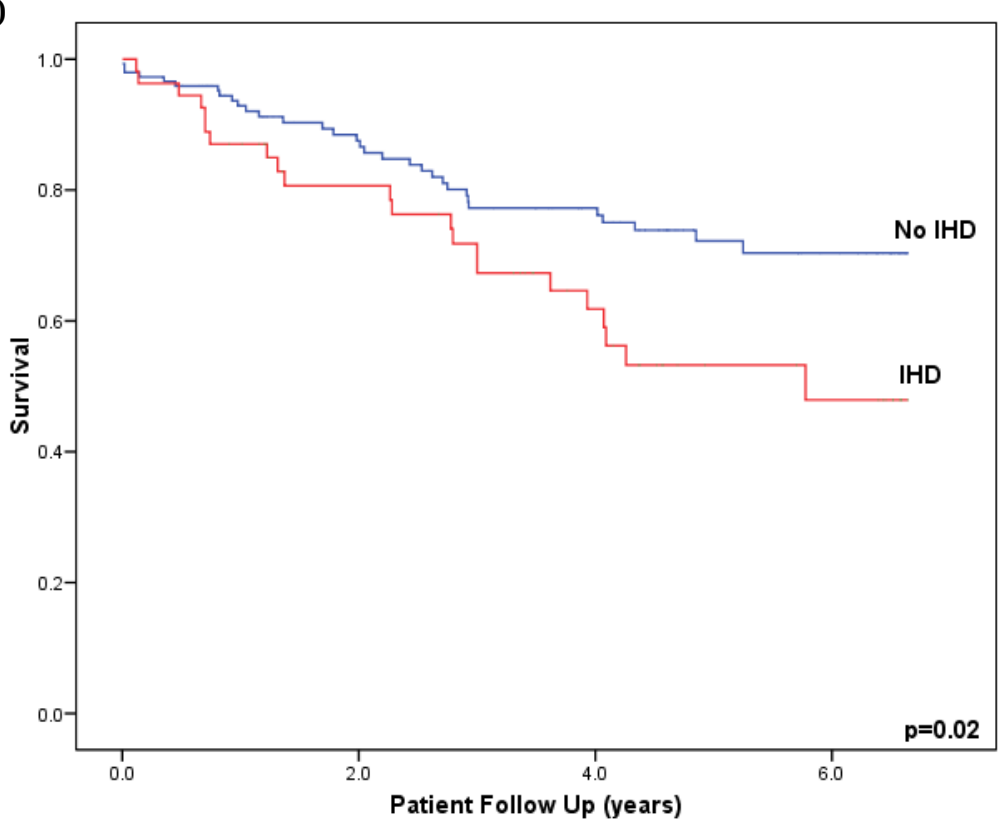
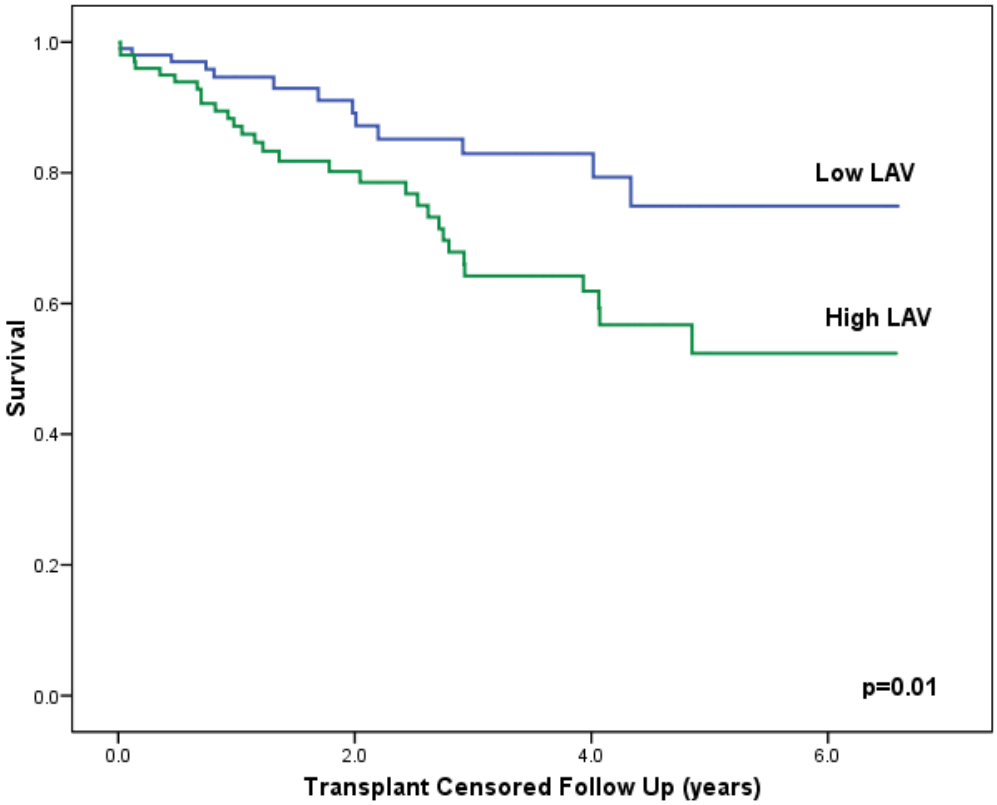


Figure 5.3 Kaplan Meier transplant censored survival curves according to (a) LAV median, (b) LVSD



(b)

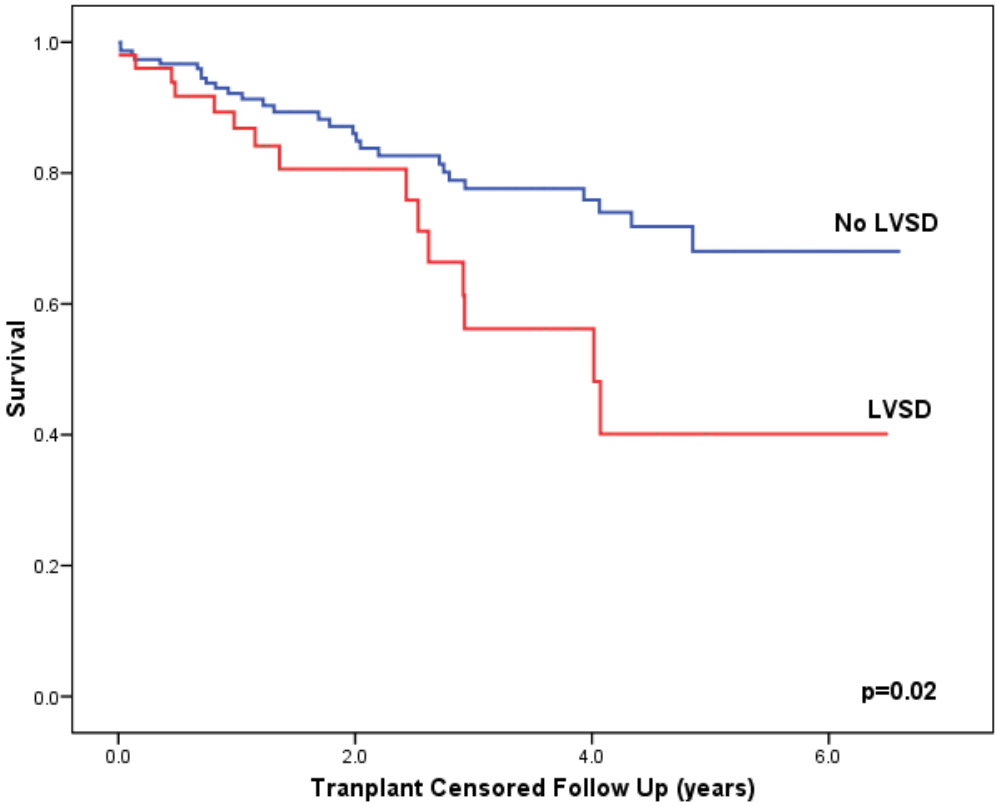
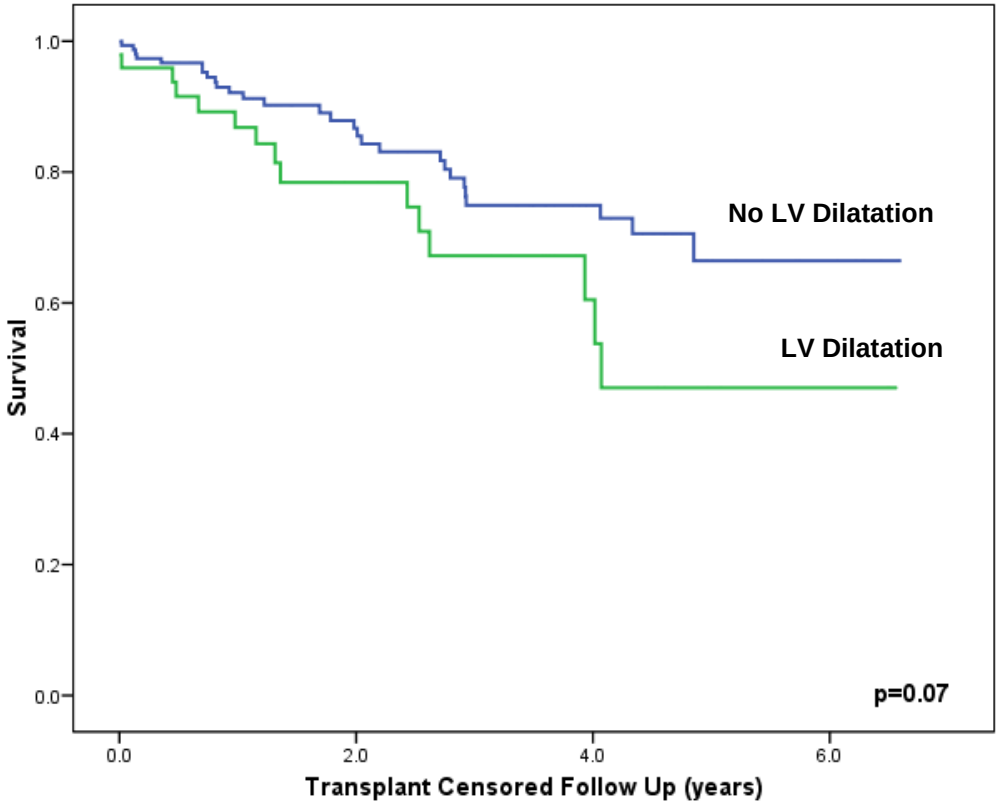
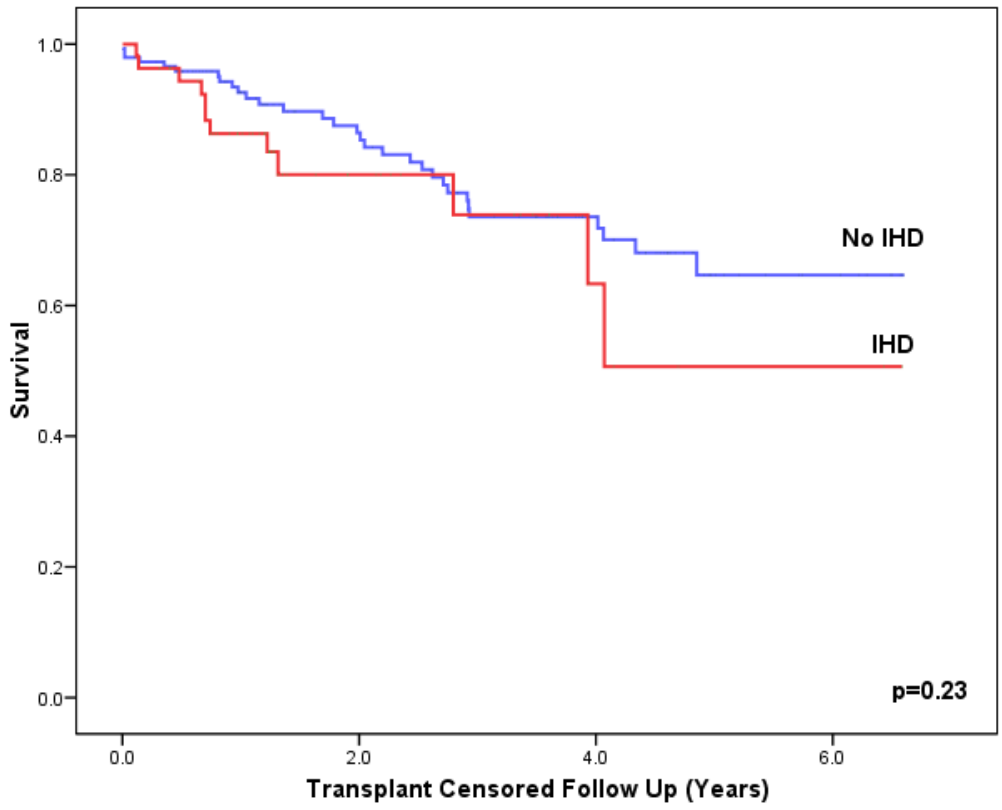


Figure 5.3 Kaplan Meier transplant censored survival curves according to c) LV dilatation and (d) past history of ischaemic heart disease

(c)



(d)



5.3.4 (c) Predictors of death

Table 5.5 shows univariate and multivariate Cox survival analyses for patient clinical and cardiac characteristics. As before, we initially performed non-transplant censored analyses. Univariate analyses showed that LVSD, LAV/BSA (absolute value or categorised according to the median) and past history of ischaemic heart disease were significantly associated with death. Advancing age increased risk of death but this did not reach statistical significance. Multivariate analysis (Table 5.5) was performed only entering one measurement of LAV (LAV ≥median or LAV/BSA). Independent predictors of mortality were LVSD, LAV/BSA or LAV ≥median and past history of ischaemic heart disease.

Transplant censored Cox survival analyses was also performed (Table 5.6). The factors significantly associated with death were LVSD and left atrial volume (corrected for BSA or categorised according to median LAV). Older age was also associated with death, but did not reach statistical significance (p=0.06). Independent predictors of death were LVSD and LAV/BSA.

		Univariate Analyses			Multivariate Analyses		
Variable		**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
LV Systolic Dysfunction		**1.98**	**1.12-3.50**	**0.02**	**1.86**	**1.05-3.28**	**0.03**
LAV/BSA greater/=median		**2.09**	**1.18-3.67**	**0.01**	**2.04**	**1.16-3.62**	**0.01**
Ischaemic Heart Disease		**1.88**	**1.09-3.23**	**0.02**	**2.02**	**1.13-3.52**	**0.01**
Mean Dose of Ultrafiltration		**1.01**	**0.63-1.63**	**0.96**			
LAV/BSA (per ml/m^2)**		**1.07**	**1.03-1.12**	**<0.01**	**		
Ejection Fraction (per %)		**0.98**	**0.97-1.00**	**0.10**			
LVMI (per g/m^2)		**1.00**	**0.99-1.01**	**0.59**			
LV Dilatation		**1.48**	**0.83-2.63**	**0.18**			
Systolic BP (per mmHg)		**1.00**	**0.98-1.02**	**0.94**			
Diastolic BP (per mmHg)		**0.99**	**0.95-1.03**	**0.76**			
Age (per year)		**1.02**	**0.99-1.05**	**0.08**			
BSA (m^2)		**0.28**	**0.08-1.10**	**0.10**			
Male Sex		**0.64**	**0.37-1.10**	**0.11**			
Diabetes Mellitus		**0.83**	**0.48-1.41**	**0.48**			
Heart Failure		**1.08**	**0.39-2.98**	**0.88**			
Cerebrovascular Disease		**1.97**	**0.84-4.62**	**0.12**			
Peripheral Vascular Disease		**1.22**	**0.52-2.84**	**0.65**			
Smoking	**Never (ref)**	**1.00**					
	Current	**1.26**	**0.64-2.48**	**0.49**			
	Ex smoker	**1.91**	**0.89-3.55**	**0.08**			

** Entering LAV/BSA instead of LAV/BSA≥ median

LV Systolic Dysfunction	**HR 1.81**	**95% CI 1.02-3.23**	**p=0.04**
LAV/BSA (per ml/m^2)	**HR 1.07**	**95% CI 1.03-1.12**	**p<0.01**
Ischaemic Heart Disease	**HR 2.23**	**95% CI 1.27-3.92**	**p<0.01**

Table 5.5 Results of univariate and multivariate Cox regression survival analyses of all patients with LVH

All-cause mortality is the dependable variable. Hazard ratios (95% confidence intervals) are shown.

		Univariate Analyses			Multivariate Analyses		
Variable		**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
LV Systolic Dysfunction		**2.12**	**1.13-3.97**	**0.02**	**1.90**	**1.01-3.58**	**0.05**
LAV/BSA greater /= median		**2.24**	**1.16-4.30**	**0.01**	**2.21**	**1.15-4.27**	**0.02**
LAV/BSA (per ml/m^2)**		**1.08**	**1.03-1.13**	**<0.01**	**		
Mean Dose of Ultrafiltration		**1.27**	**0.72-2.23**	**0.41**			
Ejection Fraction (per %)		**0.98**	**0.96-1.00**	**0.11**			
Systolic BP (per mmHg)		**1.01**	**0.99-1.04**	**0.28**			
Diastolic BP (per mmHg)		**0.98**	**0.93-1.02**	**0.27**			
LVMI (per g/m^2)		**1.00**	**0.99-1.01**	**0.63**			
LV Dilatation		**1.77**	**0.95-3.32**	**0.08**			
Age (per year)		**1.02**	**0.99-1.05**	**0.06**			
BSA (m^2)		**0.25**	**0.06-1.21**	**0.12**			
Male Sex		**1.30**	**0.67-2.44**	**0.46**			
Diabetes Mellitus		**0.91**	**0.50-1.70**	**0.77**			
Ischaemic Heart Disease		**1.51**	**0.77-2.97**	**0.23**			
Heart Failure		**1.50**	**0.54-4.27**	**0.43**			
Cerebrovascular Disease		**2.29**	**0.90-5.86**	**0.12**			
Peripheral Vascular Disease		**2.04**	**0.86-4.84**	**0.11**			
Smoking	**Never (ref)**	**1.00**					
	Current	**1.49**	**0.72-3.08**	**0.28**			
	Ex smoker	**1.84**	**0.89-3.79**	**0.09**			

** Entering LAV/BSA instead of LAV/BSA≥ median

LV Systolic Dysfunction HR 2.00 95% CI 1.06-3.76 p=0.03

LAV/BSA (per ml/m^2) HR 1.08 95% CI 1.03-1.18 p<0.01

Table 5.6 Results of univariate and multivariate Cox regression transplant censored patient survival analyses of all patients with LVH.

Results of univariate and multivariate Cox regression survival analyses of all patients with LVH; all-cause mortality is the dependable variable. Hazard ratios (95% confidence intervals) are shown

5.4 DISCUSSION

As has been stated before, LVH develops early in chronic kidney disease, with a roughly reciprocal relationship existing between renal function and LV mass (173). Most echocardiography studies indicate LVH as the commonest abnormality of uraemic cardiomyopathy, being prevalent in 70-80% of patients who commence dialysis. This figure may be an overestimate due to inaccurate measurement and calculation of LV mass using echocardiography. Nevertheless, CMR has also estimated LVH to be present in approximately 60-67% of ESRD patients confirming these early echocardiography findings (142). In addition, presence and progression of LVH are associated with poorer outcome and is an independent risk factor for cardiac tachyarrhythmias, sudden cardiac death and symptomatic heart failure in ESRD patients (89).

Whether regression of LVH in ESRD is possible, as has been demonstrated in the general population, remains controversial (213). By the identification and intervention of specific variables (such as intravascular volume, hypertension, calcium and/or phosphate), a number of small studies have demonstrated a significant reduction in LVMI. However, application of these data into clinical practice is limited due to lack of adequate controls and randomisation, small sample sizes and use of echocardiography. A greater body of evidence demonstrates persistence or worsening of LVH despite more intensive dialysis or better blood pressure and fluid control (214).

Thus, to improve cardiovascular survival in ESRD patients with LVH, alternative targets have been sought which may be amenable to intervention. In this way, well

controlled, adequately powered and randomised studies could be performed to better tailor therapeutic strategies.

Bearing this in mind, the following study was performed using CMR to assess cardiac morphology and performance. To identify independent prognostic factors of ESRD patients with LVH, clinical history and other cardiac abnormalities were included in the survival analyses. Ultimately, the strength of this study lies with the use of CMR to most accurately identify a cohort of patients with LVH for subsequent analyses. Left atrial volume was also measured and included in the prognostic modelling.

5.4.1 Left atrial volume

The left atrium performs three functions during the cardiac cycle (209) and its size changes accordingly:

1. *Isovolumetric contraction and LV systole*: receive and store blood from the pulmonary circulation.
2. *Early Diastole:* transfer blood into the left ventricle after mitral valve opening via a pressure gradient (this is represented by the "E wave" on mitral valve colour Doppler.
3. *Late Diastole:* atrial contraction augments LV stroke volume by 20% (this is represented by the "A wave" in mitral valve colour Doppler.

5.4.1(a) Measurement of LA volume

In practice and in this study, maximum LAV (just before mitral valve opening) is routinely measured. This can accurately and reproducibly be performed using 2D

echocardiography and accordingly, the American Society of Echocardiography has recommended quantification of LA volume using biplane 2D echocardiography using the area-length method. Similarly, CMR accurately estimates of LA volume using similar cine images from vertical and horizontal log axis views (156;210).

5.4.1(b) Determinants of LA size

Body size is a major determinant of LA volume, but a correction can be performed using body surface area. Gender differences in LA volume are usually accounted for by variation in body size. Furthermore, age related LA enlargement and impaired diastolic conduit function have been reported (209). As in ventricular remodelling, the atria enlarge in response to excessive pressure and volume:

- Pressure overload: LA enlargement has been demonstrated in patients with mitral valve stenosis and LV dysfunction (i.e. increased LA afterload).
- Volume overload: conditions with chronic volume overload, (valvular regurgitation, arterio-venous fistulae) and high cardiac output states (anaemia) are also associated with LA enlargement.

However, in the absence of an atrial or valvular disorder, LA volume usually reflects ventricular filling pressures. As ventricular relaxation and compliance are reduced during diastole, LA pressure rises to maintain LV filling and is accompanied by increased atrial wall tension, chamber dilatation and myocyte stretch. Thus, LA volume may be representative of the magnitude of LV diastolic dysfunction (see below). The value of LAV has been shown to represent the average effects of

chronic LV diastolic dysfunction (and hence haemodynamic control) rather than the immediate effect at the time of the study (215).

In this study, elevated left atrial volume (above median) was less common in male patients. Furthermore, female sex was an independent predictor of high LAV (≥ median) on CMR however neither sex nor BSA had any effect on survival in these analyses. Previous studies have shown removal of sex related difference in LAV when corrected for body size (see above). These previous studies had a higher proportion of females in the study cohort (between 50-67%) compared to this study (27.9%) which may have affected this analysis.

There was no significant difference in cardiovascular disease history between both groups (above or below median LAV) and heart rate, LV ejection fraction, LVMI and LV chamber size (at end diastole and systole) were similar in both groups. Similarly, E:A ratio was not significantly different between groups. This suggests that LA size was not a marker of delayed diastolic filling time or impaired LV systolic emptying. However, mean dose of ultrafiltration was significantly associated with high LAV and a significant predictor of LAV in haemodialysis patients. As discussed before, mean dose of ultrafiltration is a crude marker of fluid overload and patients with large interdialytic fluid gains most likely receive higher doses. Unfortunately, no other assessments of fluid status, such as radionuclide tagging or bio-impedance analyses, were available for this cohort especially those patients not receiving haemodialysis. However, these findings confirm previous studies, in the general population, that demonstrate a significant relationship between elevated LAV and chronic fluid overload.

5.4.2 Left ventricular diastolic dysfunction in ESRD patients

LV diastolic dysfunction can be defined as an abnormality of diastolic relaxation, filling or compliance that impairs ventricular diastolic filling. Diastolic function can be assessed using Doppler echocardiography to measure rate of LV pressure decline (isovolumetric relaxation time: IVRT) or rate and extent of LV filling (commonly using mitral inflow early (E) and late (A) ratios or more recently tissue Doppler myocardial velocity, strain and strain rate.). More invasive studies using cardiac catheterisation and angiography can be used to obtain cardiac cycle pressure-volume loops.

Expanded intravascular volume and LV hypertrophy/interstitial fibrosis are common in ESRD patients and predispose to development of LV diastolic dysfunction. Most studies have used Doppler echocardiography to quantify diastolic dysfunction in ESRD patients:

- Josephs et al demonstrated significantly impaired early diastolic filling in 100 haemodialysis patients using Doppler E:A ratio as a marker of diastolic function. In particular, older (>60 years) haemodialysis patients were at higher risk of diastolic dysfunction and diastolic function was significantly correlated with dialysis adequacy and higher blood pressure (216).

- Similarly in 25 CAPD patients, Huting et al demonstrated impaired LV diastolic dysfunction especially in patients with more severe LVH, using trans-mitral inflow velocities and colour tissue Doppler measurements (217).

- Using more invasive cardiac pressure measurements, Wizeman et al demonstrated elevated LV end diastolic pressure in 29 haemodialysis patient compared to healthy controls. Most patients had preserved systolic function and the authors concluded that reduced LV compliance and subsequent impaired diastolic filling predisposed patients to symptoms of congestive cardiac disease (218).

The data presented in this chapter do not support a role of diastolic dysfunction in LA enlargement within this patient group since there were no significant difference in E:A ratios between high and low LAV groups.

5.4.3 Left atrial volume and outcome

A number of studies in the general population have demonstrated the predictive role of elevated LA volume for adverse cardiovascular outcome. Of these, two of the largest are described below:

- Data from the Cardiovascular Health Study looking at M-Mode echocardiographic measurements and outcome in 5888 patients demonstrated higher left atrial size as an independent predictor of all cause mortality, stroke and coronary artery disease (219).
- In a sub analyses from the Framingham Heart Study (n=3099), Gajewski et al demonstrated that LA enlargement predicted higher rates of stroke and death in men, however the effect was attenuated when corrected for LV mass (220) .

In ESRD patients, two studies have demonstrated a prognostic role of LAV:

- Tripepi et al used echocardiography to measure cardiac parameters and related them to patient outcome. LAV was predicted by LVMI, LVEF, E:A ratio and antihypertensive therapy. In addition, elevated LAV corrected for height independently predicted death in this patient population (207). There was no difference in the results presented in this chapter when LAV was corrected for height as opposed to BSA.
- In a subsequent study from the same group, patients underwent repeat echocardiography. Rise in LAV/height between scans was predictive of fatal and non-fatal cardiac events compared to patients whose LAV/height remained the same. Similarly, a 1ml/m^2 increase in LAV/height was associated with a 12% increase in relative risk of a cardiovascular event (221).

5.4.4 Prognostic findings

From these data female sex, higher LAV corrected for BSA, past history of ischaemic heart disease, and LVSD on CMR were significantly associated with death during the follow up period. Aspirin use was higher in those patients who died, presumably due to the higher proportion of patients with a cardiac history in this patient group.

In the survival analysis, elevated LAV and LVSD were significantly associated with poorer survival (transplant and non transplant censored; Figure 5.2 and 5.3). Multivariate analysis showed that elevated LAV/BSA (represented as an absolute value or divided according to the median) and LVSD independently predicted death (even when censored for renal transplantation) in ESRD patients with LVH. Past history of ischaemic heart disease was a significant, independent predictor of non

transplant censored mortality and significantly reduced non transplant censored survival. Presence of LV dilatation did not have a statistically significant effect on survival. These data confirm the findings of previous studies investigating LAV and survival. However this study differs in two aspects:

- Previously, all ESRD patients were included in analyses. This study only includes patients with pre-existing features of LVH.
- This cohort has been examined using CMR to provide an accurate assessment of LV mass whereas the previous studies have used echocardiography. One should note, however, that there is no difference in assessment of LAV between both methods.

5.4.4 (a) Left atrial volume and survival

In the present study, LAV was not significantly correlated with LV mass, suggesting that elevated LA volume is not solely due to impaired atrial emptying into a large, poorly compliant LV. LAV was not associated with diastolic dysfunction in our population as measured by E:A ratio, however, measurement of other markers of LV diastolic dysfunction, such as pulmonary venous flow velocity or LV tissue Doppler would have been useful to confirm these mitral valve studies. In addition, E:A ratio is a limited marker for diastolic function at greater LA pressures due to a tendency back to normal values (also known as “pseudonormalisation”).

Thus, based on these results in ESRD patients with LVH, left atrial enlargement is largely caused by chronic fluid overload, and the associated expansion in intravascular volume. This hypothesis is supported by the finding that dose of ultrafiltration (acting as a crude marker of fluid retention) independently predicted

LAV in haemodialysis patients. Reduction of LA volume has been achieved in patients with mitral valve disease and atrial fibrillation (222;223); however its effect on overall prognosis remains unknown. Whether tight control of fluid-volume status in patients with ESRD patients similarly reduces LA volume and mortality requires controlled clinical trials in the future.

5.4.4.(b) Left ventricular systolic dysfunction and survival

Left ventricular systolic dysfunction has been associated with (often asymptomatic) ischaemic heart disease and, in turn, with poorer survival (139). This is presumably due to occlusive large vessel disease and inadequate growth of penetrating epicardial vessels in response to cardiac myocyte hypertrophy. Ventricular action potential propagation and recovery are impaired in the presence of LVH and LVSD increasing the risk of ventricular re-entrant tachyarrhythmias (51;224). The potential benefits of improving systolic function on prognosis of patients with ESRD, has been demonstrated in a number of small studies using pharmacological approaches or modification of dialysis regimens (20;124). However, these interventions are not commonly used in ESRD patients due to poor tolerance of patients or the opinions of the treating nephrologist. Hopefully, as more robust data becomes available medical practice may change in ESRD patients with myocardial dysfunction.

5.4.4 (c) Ischaemic heart disease and survival

As has been shown before, a clinical history of CV disease also reduced survival, since non-transplant censored multivariate Cox survival analyses identified past history of ischaemic heart disease as a significant, independent predictor of death. Clinical history of ischaemic heart disease did not, however, significantly, affect

transplant censored survival. These differences between transplant and non-transplant censored survival can be explained by the disproportionately high number of patients with ischaemic heart disease who subsequently underwent renal transplantation (IHD 53.7% vs. No IHD 28.6%) in this cohort. As a result of transplant censoring, there was not a statistically significant difference in survival despite Kaplan-Meier analyses demonstrated separating survival curves (Figure 5.2). This is presumably due to fewer patients in the IHD group.

5.4.5 Limitations

As before, patients recruited to this study were being assessed for renal transplantation and may not be representative of all ESRD subjects. However, since these patients are considered healthy enough to be considered for transplantation, it is likely that these results would be relevant to other patients with more significant co-morbidities. In addition, limited information was obtained regarding ventricular diastolic function in this cohort and hopefully, as more detailed methods (e.g. tissue Doppler) are utilised, these data will become available.

5.5 CONCLUSIONS

In conclusion, in ESRD patients with LVH, elevated LAV and presence of LVSD are independent predictors of death and may provide novel factors that may be amenable to modification to improve cardiovascular prognosis. Elevated LAV is due, in part, to fluid overload which may be a useful target in the future.

Chapter 6

A study of Microvolt T Wave Alternans in ESRD patients

6.1 INTRODUCTION

As has been discussed in Chapter 1, patients with end stage renal disease (ESRD), including those receiving or close to requiring dialysis, have a significantly increased risk of premature cardiovascular death. In contrast to the general population, where myocardial ischaemia and infarction (MI) are the leading cause of cardiovascular death, ESRD patients are significantly more likely to develop cardiac (commonly ventricular) tachyarrhythmias and sudden cardiac death (SCD). Factors associated with SCD include myocardial structural abnormalities of uraemic cardiomyopathy and accelerated coronary artery disease. In addition, factors such as large electrolyte fluctuations, bone mineral disease, uraemia, autonomic dysfunction and inflammation have also been implicated in the development of SCD. However, despite elucidation of potential risk factors for ventricular tachyarrhythmias (VTA), identification of high risk ESRD patients and primary prevention of SCD has proven difficult. Furthermore, treatment of traditional cardiovascular risk factors (eg dyslipidemia) has shown little survival benefit (26;81).

A similar problem exists in patients with symptomatic heart failure and impaired LV systolic function. Results from MADIT II and SCD- Heart Failure Trial show significant survival benefit using implantable cardioverter defibrillators (ICD) for primary prevention of SCD in patients with ischaemic and non-ischaemic cardiomyopathy (82; 83). However many of these ICDs remain unused and current estimates suggest that to prevent one SCD, 18 devices require to be inserted. Additional electrophysiological tests have been evaluated to better identify higher risk patients who would benefit from ICD insertion.

Microvolt T Wave Alternans (MTWA; HearTwave II system, Cambridge Heart, Bedford, Massachusetts) is a novel, non-invasive technique of assessing VTA risk in patients. The principles of MTWA have been discussed in Chapter 1. MTWA measures beat-to-beat variations in standard 12-lead ECG T-wave morphology, indicating unstable ventricular repolarisation. Several large prospective trials have demonstrated that MTWA analysis is superior or comparable to other more invasive electrophysiological methods of independently predicting (negatively and positively) patients at risk of VTA or SCD. These studies included patients with ischaemic heart disease, biventricular cardiac failure and implantable cardiac defibrillators. In patients with symptomatic ischaemic cardiomyopathy, the prevalence of abnormal MTWA result varies between 64 and 72% (105;161;225). Furthermore, in diabetic patients with no symptoms of cardiovascular disease, abnormal result has been found in 25.4% of patients which is significantly higher when compared to normal healthy controls (5.7%) (111;226). No such studies have been performed in ESRD patients.

In this study, two hundred patients with ESRD and 30 control patients with hypertensive LVH were assessed using MTWA. The aims of this study were to:

- Determine prevalence of abnormal MTWA in ESRD patients compared to patients with hypertensive LVH and normal renal function.
- Determine associations between features of uraemic cardiomyopathy and MTWA result.

6.2 METHODS

6.2.1 Patients

ESRD patients already established on or within 6 months of requiring renal replacement therapy (RRT) were consecutively assessed. In addition, hypertensive patients with evidence of LVH on echocardiography or ECG and normal renal function (measured within 6 months of recruitment) were also entered into the study as controls (termed LVH patients).

All patients underwent cardiovascular risk factor assessment including history, clinical examination, ECG as well as routine haematological, biochemical and lipid profile. CMR was performed to measure left ventricular (LV) mass and function followed by MTWA testing. Patients with contraindication to CMR (e.g. presence of permanent pacemaker or ferromagnetic implants, severe claustrophobia, pregnancy) were not entered into the study. Furthermore, patients with atrial fibrillation were excluded as irregular R-R intervals confound frequency analysis during MTWA testing.

6.2.2 CMR acquisition and analyses

CMR scans were acquired for assessment of LV mass and function and analysed as described in Chapter 2. Patients were classified as having LVH, LVSD or LV dilatation based on previously described normal values.

6.2.3 MTWA testing

Preparation, acquisition, analyses and classification of MTWA testing have been described in detail in Chapter 2. Based on previously published studies, we further classified results as "abnormal" for positive and indeterminate test results and negative tests as "negative". If initially an indeterminate result was obtained, immediate retesting was attempted. The reason for indeterminate test was also provided by the analysis software (227).

6.2.4 Statistical analyses

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc. Illinois, USA). Data are described as mean±standard deviation. Data were compared by chi-squared or Fisher's test for categorical data and paired t-test for continuous data. Simple followed by multivariate logistic regression analyses were performed to identify individual predictors of abnormal MTWA result. BNP underwent logarithmic transformation to allow parametric statistical comparison. Survival data including survival time (mean± standard deviation) are shown as Kaplan-Meier graphs (with statistical comparison using the log rank test).

6.3 RESULTS

6.3.1 Patient demographics

Two hundred ESRD patients and 30 LVH patients were assessed. Table 6.1 shows the clinical and cardiac data for ESRD and LVH patients.

6.3.2 Comparison between ESRD and LVH patients

There were no statistically significant differences between age, sex, BMI, and systolic blood pressures between each group. Interestingly, diastolic blood pressure was significantly higher in the LVH group compared the ESRD group. As one would expect, there was a significantly higher frequency of traditional cardiovascular risk factors in ESRD patients compared to patients with LVH. This difference is also reflected in the medications these patients were taking.

LV systolic function was preserved in both groups. Cardiac data demonstrated a lower ejection fraction and higher LVMI and LV chamber size in the ESRD group compared to LVH patients, although these did not reach statistical significance. Presence of LVH was high in both groups and despite LVH patients being recruited based on previous echocardiography and ECG, only 18 (60%) had LVH on CMR. LVSD and LV dilatation was also more common in ESRD patients, but similarly this did not reach statistical significance.

Microvolt T wave alternans result was negative for 85 (42.5%), positive for 44 (22%) and indeterminate in 71 (35.5%) in ESRD patients. In the LVH group of patients, MTWA was negative in 22 (73.3%), positive in 3 (10%) and indeterminate in 5 (16.7%) of patients (Figure 6.1). On comparison, abnormal MTWA result was significantly more common in ESRD compared to LVH patients (ESRD 57.5% vs. LVH 26.7%; p=0.002; Table 6.1).

Reasons for indeterminate tests in ESRD patients (Figure 6.2) were failure to achieve heart rate between 105 and 110bpm for ≥1min (50.7% of all indeterminate results),

excessive ventricular ectopy during exercise (23.9%), a noisy recording (21.1%) and rapid rise through target heart rate of 105-110bpm or unsustained MTWA (≤1 min; 4.2%). In LVH patients, 5 indeterminate tests were due to failure to achieve heart rate rise (2 patients) and to noisy recording (3 patients).

Variable	ESRD N=200	LVH Only N=30	p
MTWA abnormal	**115(57.5)**	**8 (26.7)**	**<0.01**
Age (years)	56.3(±12.7)	53.1 (±10.7)	0.21
Male (%)	142 (71)	25 (83.3)	0.16
BMI (kg/m^2)	26.5(4.7)	27.1(4.9)	0.19
Systolic BP (mmHg)	146 (±24.1)	152 (±22.5)	0.17
Diastolic BP (mmHg)	**82 (±14.2)**	**89(±11.1)**	**0.01**
Renal Replacement Therapy			
HD	118 (59.0)	-	
PD	17 (8.5)	-	
CKD 5	65 (32.5)	-	
RRT Time	1.14 (2.1)	-	
Primary Renal Disease			
Diabetic Nephropathy	46 (23.0)	-	
APCKD	20 (10.0)	-	
Glomerulonephritis	42 (21.0)	-	
Renovascular Disease	16 (8.0)	-	
Chronic Pyelonephritis	20(10.0)	-	
Other	26 (13.0)	-	
Unknown	30 (15.0)	-	
Clinical History			
Diabetes mellitus	**54 (27.0)**	**0**	**<0.01**
Ischemic Heart Disease	**49 (24.5)**	**2(9.5)**	**<0.01**
Heart failure	15 (7.5)	1 (3.3)	0.70
Cerebrovascular disease	26 (13)	1(3.3)	0.22
Peripheral vascular disease	**35 (17.5)**	**0**	**0.01**
Dyslipidaemia	**117 (58.5)**	**10 (33.3)**	**0.01**
Smoking Never	89 (44.5)	19 (61.9)	0.08
Current	54 (27.0)	3 (10)	
Ex	57 (28.5)	8 (26.7)	
Drug History			
Epo receptor Agonist	**162 (81.0)**	**0**	**<0.01**
β Adrenoceptor Blocker	92 (46.0)	10 (33.3)	0.15
Aspirin	**102 (51.0)**	**3 (10)**	**0.01**
Warfarin	13 (6.5)	0	0.23
Clopidogrel	17 (8.5)	0	0.16
ACEI/ARB	91 (45.5)	12 (40.0)	0.51
Diuretic	58 (29)	6 (20.0)	0.54
Nitrate	15 (7.5)	8(26.7)	<0.01
Calcium Channel Blocker	76 (38.0)	8(26.7)	0.19
α Adrenoceptor Blocker	24 (12.0)	1 (3.3)	0.09
Statin	**125 (62.5)**	**9(30.0)**	**<0.01**
CMR Results			
Ejection Fraction (%)	61.9 (±15.3)	65.8(±11.5)	0.19
Myocardial mass/BSA	93.3 (±38.2)	82.0(±32.9)	0.13
EDV/BSA (ml/ m^2)	68.9(±35.6)	67.1(±13.7)	0.79
ESV/BSA (ml/ m^2)	28.7(±26.2)	23.5(±12.4)	0.08
LVH on MRI	124 (62.0)	18 (60.0)	0.87
LVSD on MRI (EF<55%)	45 (22.5)	4 (13.8)	0.34
LV dilation	19 (9.5)	2 (6.9)	0.65

Table 6.1 Clinical, drug and cardiac data for patients.

Comparisons between ESRD and LVH patients are shown.. Data are number with percentage in parentheses or mean ± standard deviation except for RRT time where median and interquartile range are shown .

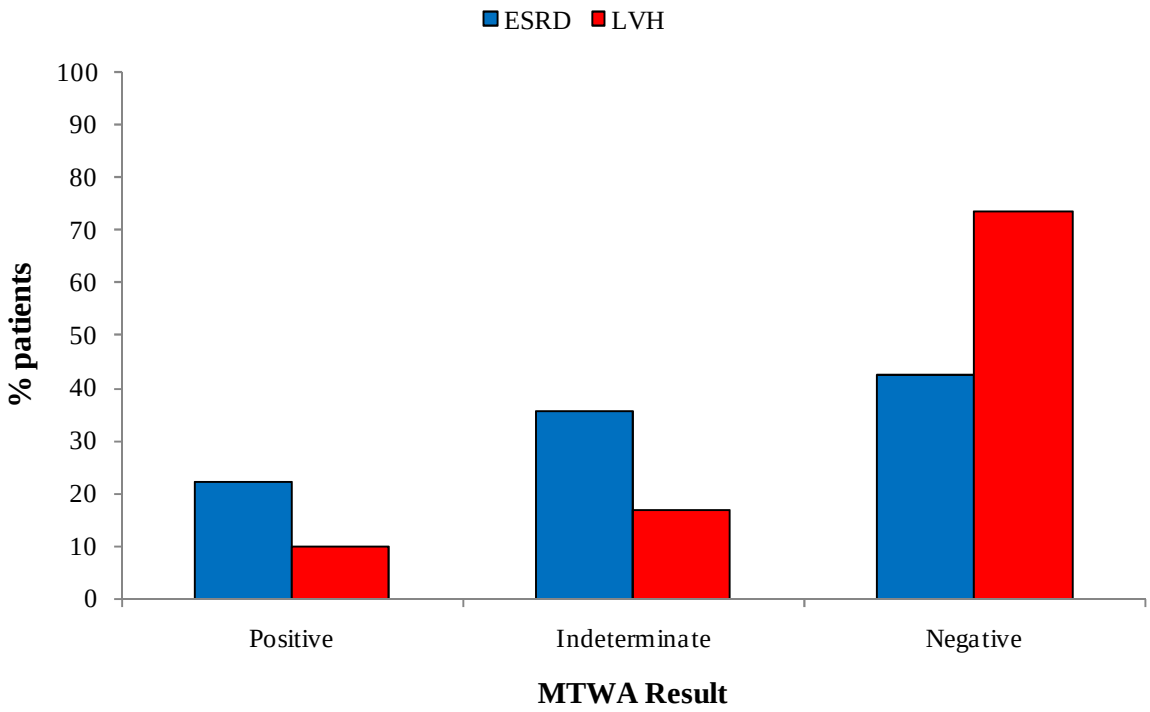


Figure 6.1 Comparison of MTWA result of ESRD and LVH patients. Data labels are percentage in each patient group.

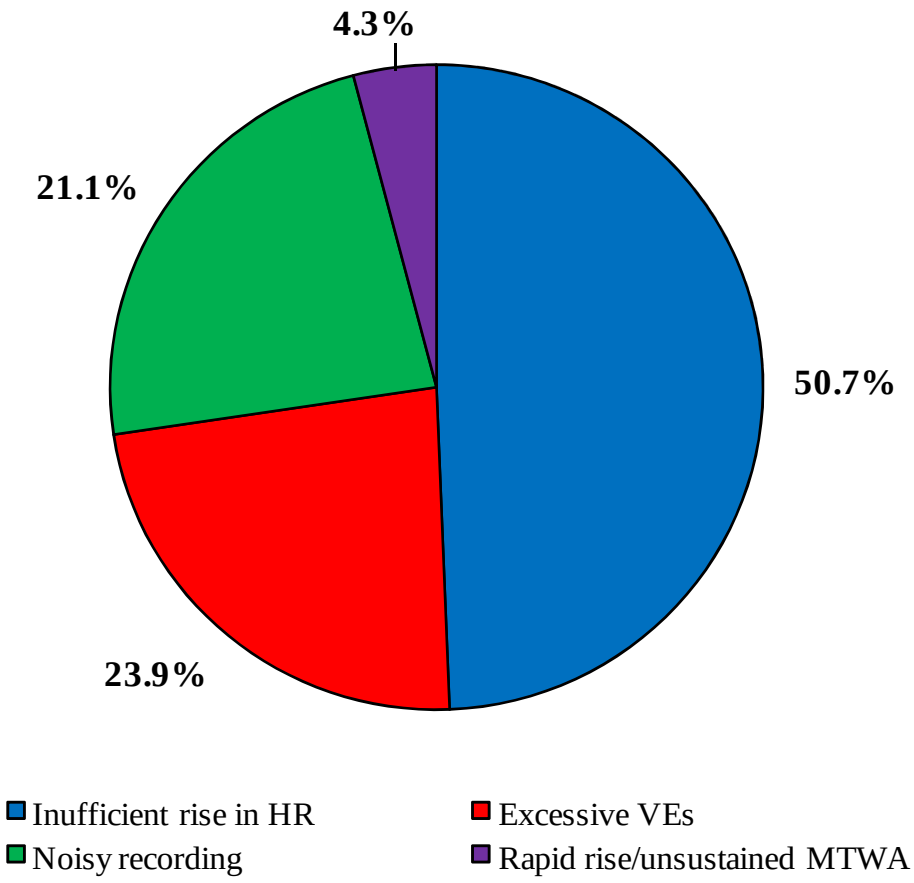


Figure 6.2 Cause of Indeterminate MTWA result in ESRD patients only. HR= heart rate, VE= ventricular ectopics

6.3.3 Factors associated with abnormal MTWA result

In the ESRD group, abnormal MTWA (Table 6.2) result was significantly associated with older age and receiving haemodialysis as RRT. Furthermore, those patients with current or past cardiovascular morbidity were more likely to have an abnormal MTWA result. There was a significant association between an abnormal result and diabetic nephropathy or renovascular disease as primary renal disorder, past medical history of diabetes mellitus, ischaemic heart, cerebrovascular or peripheral vascular disease, and dyslipidaemia. In addition, abnormal result was significantly associated with statin therapy.

To assess the effect of blood parameters on MTWA result, venepuncture was performed 10- 15 minutes before testing (Table 6.2). There was no significant difference between measured serum cations (namely potassium and calcium), haemoglobin, fibrinogen, inorganic phosphate, PTH, inflammatory markers, and troponin I between both groups. Random plasma glucose and glycosylated haemoglobin were significantly higher in patients with an abnormal MTWA result, presumably as a result of higher proportion of diabetic patients in this group. Brain natriuretic peptide was also significantly higher in the abnormal MTWA group. Total plasma cholesterol was significantly lower in patients with an abnormal MTWA result.

The associations between LV structural abnormalities of uraemic cardiomyopathy and MTWA result were assessed (Table 6.3). Abnormal MTWA result was significantly associated with abnormalities of uraemic cardiomyopathy: higher LV mass, lower ejection fraction and higher EDV/BSA and ESV/BSA. In addition,

there were significantly higher proportions of patients with LVH and LV dilatation in the abnormal MTWA group. More patients had LVSD in the abnormal MTWA group but this did not achieve sufficient statistical significance (p=0.08).

6.3.4 Variables associated with abnormal MTWA result in ESRD patients

Logistic regression analyses were performed to determine variables independently associated with abnormal MTWA result in ESRD patients only (Table 6.4). In our model (R^2=0.40), entering only factors found to be significant after univariate analyses, increasing age and past clinical history of coronary, peripheral vascular and cerebrovascular diseases were independently associated with abnormal MTWA result. In addition, increasing LVMI (or presence of LVH) was independently associated with abnormal MTWA result. Presence of LV dilatation was associated with abnormal result but did not achieve statistical significance.

6.3.5 Effect of abnormal MTWA result on patient outcome

There were 16 deaths during a median follow up of 1.9 years (IQR 1.5, 2.6 years). Abnormal MTWA was associated with a higher number of deaths compared to negative MTWA result (12 deaths vs. 4 deaths; p=0.15) although this did not reach statistical significance. Furthermore, abnormal MTWA result was associated with a trend toward reduced survival compared to negative MTWA (Figure 6.3).

Variable		MTWA Negative N=85 (42.5)	MTWA Abnormal N=115 (57.5)	p
Age (years)		52.4(12.8)	59.1(12.0)	<0.01
Male (%)		59 (69.4)	83(72.2)	0.67
BMI (kg/m^2)		26.9 (4.8)	26.2(4.6)	0.29
BSA (m^2)		1.89(0.2)	1.87 (0.2)	0.45
Systolic BP (mmHg)		144 (23.2)	147 (24.8)	0.29
Diastolic BP (mmHg)		83(12.9)	82 (15.2)	0.52
Renal Replacement Therapy		1.17 (1.7)	1.1 (2.4)	0.67
HD		41 (48.2)	77(67.0)	<0.01
PD		11 (12.9)	6 (5.2)	0.09
Predialysis		33 (38.8)	32 (27.8)	0.10
RRT Time (years)		1.2 (0.6,2,4)	1.2 (0.6, 2.4)	0.97
Primary Renal Disease				
Diabetic Nephropathy		13 (15.3)	33 (28.7)	0.02
APCKD		12 (14.1)	8(7.0)	0.10
Glomerulonephritis		23 (27.1)	19 (16.5)	0.07
Renovascular Disease		3(3.5)	13 (11.3)	0.05
Chronic Pyelonephritis		11 (12.9)	9 (7.8)	0.23
Other		9 (10.6)	17 (14.8)	0.38
Unknown		14 (16.5)	16 (13.9)	0.62
Diabetes mellitus		16 (18.8)	38 (33.0)	0.03
Ischaemic Heart Disease		8 (9.4)	41 (35.7)	<0.01
Hypertension		73 (85.9)	105 (91.3)	0.23
Heart failure		4 (4.7)	11 (9.6)	
Cerebrovascular disease		3 (3.5)	23 (20)	<0.01
Peripheral vascular disease		4 (4.7)	31 (27)	<0.01
Dyslipidaemia		42 (49.4)	75(65.2)	0.03
Smoking	Never	45 (52.9)	44 (38.3)	0.12
	Current	20 (23.5)	34 (29.6)	
	Ex	20 (23.5)	37 (32.2)	
Epo receptor Agonist		64 (75.3)	98 (85.2)	0.08
β Adrenoceptor Blocker		26 (30.6)	46(40)	0.10
Aspirin		41 (48.2)	61 (53.0)	0.50
ACEI/ARB		41 (47.1)	51 (44.3)	0.25
Diuretic		29 (34.1)	29 (25.2)	0.17
Nitrate		3 (3.5)	12 (10.4)	0.07
Calcium Channel Blocker		28 (32.9)	48 (41.7)	0.21
α Adrenoceptor Blocker		12 (14.1)	12 (10.4)	0.43
Statin		46 (54.1)	79 (68.7)	0.04
Haemoglobin (g/dL)		11.4 (1.8)	11.4 (1.8)	0.96
Fibrinogen (g/L)		4.34 (1.1)	4.25 (1.0)	0.58
ESR (mm/h)		28 (9.5,49.0)	31(14.5, 44.0)	0.74
CRP (mg/L)		4.9(2.0, 9.9)	5.3 (3, 14)	0.08
Adjusted Ca^{2+}(mmol/L)		2.39 (0.4)	2.40 (0.2)	0.87
PO_4 (mmol/L)		1.69 (0.5)	1.56 (0.5)	0.08
PTH (pmol/L)		27.1(14.7, 50.7)	28.6(15.2,46.4)	0.99
Glucose (mmol/L)		5.3 (2.4)	5.9 (2.7)	0.02
HbA1c (%)		5.2 (1.0)	5.4 (1.5)	0.03
Potassium (mmol/L)		4.7(0.7)	4.7 (0.8)	0.76
BNP (ng/L)		174(45, 340)	335 (129,1340)	<0.01
LogBNP		2.21(±0.6)	2.61(0.7)	<0.01
Cholesterol (mmol/L)		4.61 (1.3)	4.23 (1.1)	0.04
Triglyceride (mmol/L)		1.7 (0.9)	1.6 (0.9)	0.46
HDL- Chol (mmol/L)		1.4 (0.8)	1.4(0.8)	0.28
LDL- Chol (mmol/L)		2.4(1.3)	2.2 (1.3)	0.14
Troponin I (µg/L)		0.01 (0.05)	0.03(0.07)	0.23

Table 6.2 Comparisons of clinical and blood results between patients are shown based on MTWA result.

Data are number with percentage in parentheses and mean ± standard deviation except for ESR, CRP, PTH and BNP where median and interquartile range are shown

Variable	MTWA Negative N=85 (42.5)	MTWA Abnormal N=115 (57.5)	p
Ejection Fraction (%)	**65.1 (11.4)**	**59.5 (17.3)**	**0.01**
Myocardial mass/BSA	**84.9 (33.1)**	**99.7 (40.6)**	**<0.01**
EDV/BSA (ml/ m^2)	**60.6 (22.6)**	**75.2 (41.8)**	**<0.01**
ESV/BSA (ml/ m^2)	**22.4 (14.2)**	**33.5 (31.7)**	**<0.01**
SV/BSA (ml/m^2)	**38.2 (13.5)**	**41.6 (21.9)**	**0.21**
LVH on MRI	**46 (54.1)**	**78 (67.8)**	**0.05**
LVSD on MRI (EF<55%)	**14 (16.5)**	**31 (27.0)**	**0.08**
LV dilation	**2 (2.4)**	**17 (14.8)**	**<0.01**

Table 6.3 Comparisons of CMR data between patients are shown based on MTWA result.

Data are number with percentage in parentheses or mean ± standard deviation. Tests of significance are t-test and Chi-square.

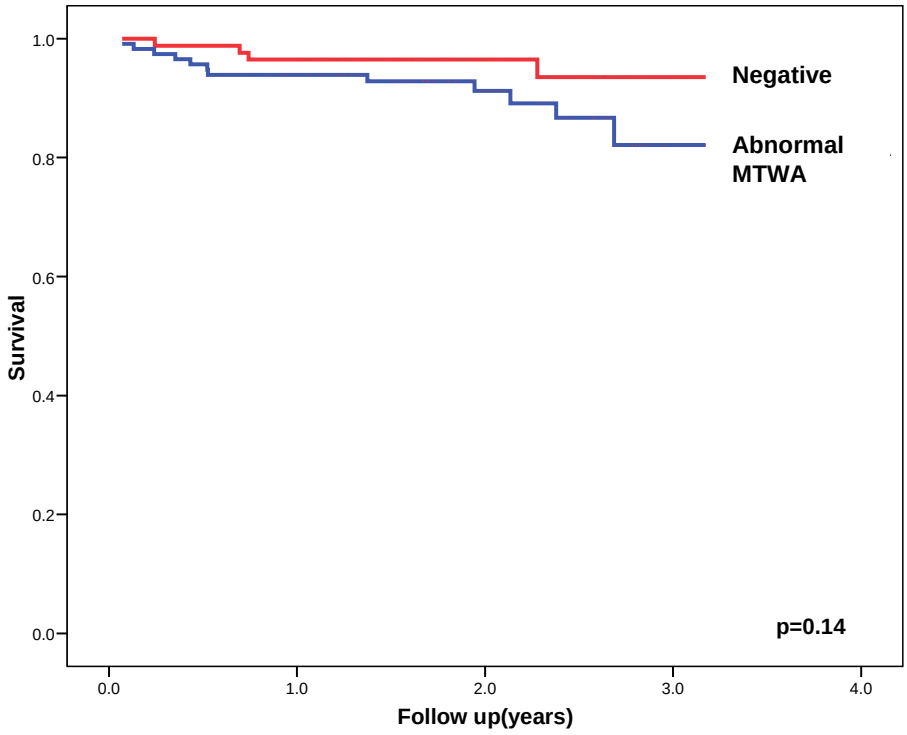
	Univariate Analyses			Multivariate analyses		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**P**
Age (per year)	**1.04**	**1.02,1.07**	**<0.01**	**1.04**	**1.01,1.07**	**0.01**
Ischaemic Heart Disease	**6.19**	**2.74,13.94**	**<0.01**	**3.24**	**1.31,8.02**	**0.01**
Cerebrovascular Disease	**6.83**	**1.98,23.60**	**<0.01**	**5.81**	**1.56,12.87**	**<0.01**
Peripheral Vascular Disease	**7.47**	**2.53,22.11**	**<0.01**	**5.34**	**1.68,16.96**	**<0.01**
LVH	**1.79**	**1.01,3.18**	**0.05**	**†2.01**	**1.01,4.03**	**0.05**
LV Dilation	**7.20**	**1.62,32.07**	**0.01**	**4.34**	**0.98,21.90**	**0.06**
Log BNP	**2.66**	**1.45,4.87**	**<0.01**			
Glucose (per mmol/L)	**1.10**	**1.02,1.19**	**0.01**			
Ejection fraction (per %)	**0.98**	**0.95,0.98**	**0.01**			
LVMI (per g/m^2)	**1.01**	**1.00,1.02**	**0.01**	**† 1.02**	**1.01,1.02**	**0.02**
LVSD	**1.87**	**0.93,3.79**	**0.08**			
Diabetes Mellitus	**2.12**	**1.09,4.15**	**0.03**			
Hypercholesterolemia	**1.92**	**1.08,3.40**	**0.03**			
Renal Replacement Therapy						
Predialysis	**1.00**					
PD	**0.57**	**0.19,1.70**	**0.31**			
HD	**1.93**	**1.05,3.59**	**0.04**			
RRT Time (per year)	**1.10**	**0.91,1.33**	**0.30**			
Sex (Male vs. Female)	**1.06**	**0.59,1.90**	**0.84**			
BMI (per kg/m^2)	**0.97**	**0.92,1.03**	**0.36**			
Systolic BP (per mmHg)	**1.01**	**0.99, 1.02**	**0.07**			
Diastolic BP (mmHg)	**0.97**	**0.95, 1.00**	**0.06**			
Pulse Pressure	**1.02**	**0.99,1.03**	**0.07**			
Chronic Heart Failure	**2.14**	**0.65,6.97**	**0.21**			
Smoking Never	**1.00**					
Current	**1.73**	**0.88,3.47**	**0.12**			
Ex	**0.70**	**0.95,3.75**	**0.09**			
Haemoglobin (per g/dL)	**1.02**	**0.86,1.18**	**0.96**			
Fibrinogen (per g/L)	**0.92**	**0.70,1.23**	**0.58**			
ESR (per mm/h)	**0.99**	**0.98,1.01**	**0.83**			
CRP (per mg/L)	**1.01**	**0.99,1.02**	**0.62**			
Adjusted Ca^{2+} (per mmol/L)	**1.08**	**0.41,2.85**	**0.86**			
PO_4 (per mmol/L)	**0.60**	**0.34,1.07**	**0.08**			
PTH (per pmol/L)	**0.99**	**0.98,1.01**	**0.42**			
HbA1c (per %)	**0.99**	**0.98,1.01**	**0.48**			
Potassium (per mmol/L)	**0.94**	**0.63,1.40**	**0.76**			
BNP (per ng/L)	**1.02**	**1.01,1.04**	**<0.01**			
Cholesterol (per mmol/L)	**0.60**	**0.32,1.17**	**0.13**			
Triglyceride (per mmol/L)	**1.12**	**0.69,1.81**	**0.67**			
HDL- Chol (per mmol/L)	**1.34**	**0.70,2.57**	**0.38**			
LDL- Chol (per mmol/L)	**1.17**	**0.63,2.16**	**0.62**			
Troponin I (per µg/L)	**12.15**	**0.02,32.8**	**0.26**			
EDV/BSA (ml/ m^2)	**1.00**	**0.98,1.02**	**0.64**			
ESV/BSA (ml/ m^2)	**1.02**	**0.98,1.04**	**0.21**			

Table 6.4 Simple (left) followed by backward stepwise (conditional) multiple logistic regression analyses (R^2=0.40) demonstrating independent predictors of abnormal MTWA result.

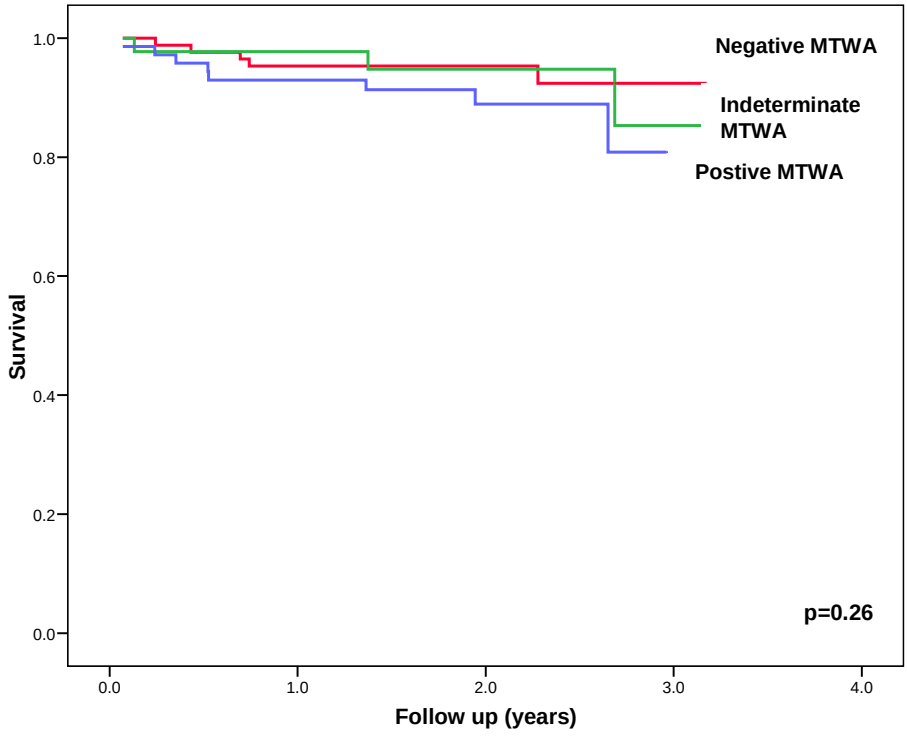
Only variables found to be significant on univariate analyses were entered into the multivariate model. †LVMI or LVH were entered individually in the model.

Figure 6.3 Kaplan Meier survival curve of ESRD patients based on MTWA result based on (a) abnormal/negative classification and (b) automated result

(a)



(b)



6.4 DISCUSSION

As has been discussed in Chapter 1, premature cardiovascular death is the commonest cause of death in patients with ESRD including those receiving or within 6 months of requiring renal replacement therapy. According to the USRDS (4; 228), the commonest causes of death in ESRD and dialysis patients are cardiac arrhythmia and cardiac arrest accounting for between 60-65% of cardiac and 20-25% of all deaths.

Findings from the "Deutsche Diabetes Dialyse Studies (4D)" and "A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)" trial have highlighted significant differences in cardiovascular disease between dialysis patients and the general population (25;26).

- The 4D study was a prospective randomised controlled trail investigating the effect of atorvastatin therapy on cardiovascular outcome in 1225 type 2 diabetic haemodialysis patients. Although LDL cholesterol was reduced, there was no statistical significant reduction of the composite primary endpoint (death from all cardiac causes, fatal stroke, non fatal MI, or non fatal stroke). Post hoc analyses, however, revealed that adjudicated deaths due to coronary artery disease only accounted for 9% of deaths and sudden death accounted for 26% of all cause mortality (25).
- In the AURORA trial, a prospective randomised study investigating therapy with rosuvastatin in 2776 haemodialysis patients, LDL cholesterol was reduced by 43% in

the therapy arm but there was no significant effect on primary outcome (adjudicated death from cardiovascular causes, non fatal MI, non fatal stroke). In the rosuvastatin treated group, death from cardiovascular cause occurred at a rate of 7.2 events/100 patient-years compared to 7.3 events/100 patient–years in the placebo group (p=0.97) and death from definite coronary heart disease was not significantly different (26).

Both of these studies, in combination with previous interventional studies, suggest that in non-ESRD population, coronary atherosclerosis causes myocardial ischaemia/infarction which may lead to sudden cardiac death. However in ESRD patients, sudden cardiac death is not as greatly influenced by coronary artery disease compared to the general population. Alternatively, these data may suggest that CAD in ESRD patients does not respond to statin treatment.

6.4.1 Factors associated with sudden cardiac death in ESRD

The presence of stable VTAs on ambulatory ECG monitoring has been shown to increases risk of SCD in the general population (99). Ventricular tachyarrhythmia development is commonly due to the interaction of abnormal myocardial substrate and aetiological triggers which interfere with normal, uniform cardiac action potential propagation and myocardial repolarisation. In the general population, transient myocardial ischaemia or areas of post MI scarring commonly produce areas of slowed ventricular action potential conduction, non-uniform depolarisation/repolarisation, and increase risk of re-entry and VTA. In patients with preserved LV function, these arrhythmias have only a small haemodynamic effect.

However, if patients have compromised myocardial function, haemodynamic effects may be great and may lead to degeneration of depolarisation wavefront and ventricular fibrillation. ESRD patients are at risk of unique factors that affect substrate (myocardium) and triggers that have been discussed in more detail in Chapter 1. Briefly these features include:

1. **Changes in myocardial structure and function (substrate)**:

   Including features of uraemic cardiomyopathy, accelerated coronary artery disease and fluid overload induced myocardial stretching.

2. **Changes in myocardial environment (trigger)**:

   Including fluctuations/imbalances in extracellular electrolyte concentrations, uraemia, anaemia, inflammation and autonomic imbalance.

6.4.2 Reducing risk of sudden cardiac death in ESRD patients

Ideally, reduction of sudden cardiac death in ESRD patients should be achieved by identification of individuals at high risk and implementation of therapy shown to reduce cardiac events with randomised prospective trials. Unfortunately, studies in this area have provided limited data due to under powering, absence of sufficient controls, or the retrospective nature of their design. However, a number of promising studies have identified therapeutic agents that may reduce VTA and SCD in ESRD patients.

- *Beta adrenergic receptor blockers*

  In a small prospective study, Cici et al randomised 144 haemodialysis patients with dilated cardiomyopathy to receive carvedilol or placebo. Prevalence of

cardiovascular death after 2 years was 29.3% in the carvedilol group compared to 67.9% in the placebo group. In addition, there was a trend to reduced SCD (carvedilol 3.4% vs placebo 10.6%) but did not achieve statistical significance due to inadequate numbers (120). Further studies are required to determine whether β blockers similarly reduce SCD in ESRD patients with normal LV function and structure.

In post MI studies (CAPRICORN and COPERNICUS), patients with mild to moderate CKD also showed marked reduction in cardiovascular death when treated with carvedilol compared to placebo suggesting that blockade of sympathetic nervous system at early stages of CKD may provide some benefit (229;230).

- *Renin angiotensin system blockers*

  There are no studies to prospectively evaluate the role of ACE inhibitors or angiotensin receptor blockers (ARBs) in ESRD patients with SCD as a primary outcome. In addition, no interventional studies have been performed in ESRD patients with reduced LV function. Small observational studies have demonstrated a significant reduction in mortality, independent of blood pressure reduction in dialysis patients treated with ACE inhibitors (231). However, a prospective trial with fosinopril found no difference in fatal and non fatal cardiovascular events between treatment and placebo group. A small prospective study of candersartan showed a reduction in cardiac arrhythmias and cardiovascular events in haemodialysis patients. However, this result was not statistically significant due to small event numbers (123;125).

Nonetheless, ACEI/ARBs are attractive therapies, if tolerated, due to their multiple effects demonstrated in non renal populations (i.e. effects on neurohumoral activation, vascular haemodynamics, myocardial architecture, vascular inflammation and oxidative stress).

- *Aldosterone receptor blockers*

  In patients with severe symptomatic heart failure, spiranolactone has been shown to significantly reduce cardiovascular death and SCD (RALES study) (232). In addition, aldosterone may contribute to myocyte hypertrophy and fibrosis in ESRD patients and earlier stages of CKD (233) and is an attractive target for intervention. Most clinicians will not prescribe these agents to dialysis patients due to risk of hyperkalaemia. In a recent prospective study of spiranolactone in 30 haemodialysis patients, no patients developed serum $K^+ > 6.0$mmol/l and only two patients required alteration in dialysate suggesting that this recognised side effect can be accommodated if necessary. Unfortunately this study demonstrated no effect on LVMI measured by CMR after 9 months of spiranolactone therapy (234).

- *Implantable cardioverter defibrillators (ICD).*

  In patients with reduced LV ejection fraction, secondary prevention with ICD insertion has been associated with reduced mortality (82). Studies which have investigated beneficial effects of ICD in dialysis patients have already been discussed in Chapter 1.

  In addition, some investigators believe that the survival benefit afforded by primary ICD insertion patients may be negated in patients with significant co-morbid

conditions such as ESRD. For example, in a retrospective study of 585 patients (235) who received ICDs, survival in dialysis patients was significantly reduced compared to patients with normal renal function patients, despite receiving dialysis being a significant predictor of ICD discharge (HR 2.30 95% CI 1.20-4.50).

In secondary prevention of VTA, data from the USRDS have demonstrated a significant (42%) reduction in mortality in dialysis patients who receive ICDs (128). Unfortunately, this study also reported that only 8% of dialysis patients who met criteria for ICD insertion as secondary prevention of SCD had a device fitted. Underutilisation of ICDs may be due to recent data reporting higher complication rates (bleeding, infection) in dialysis patients and problems when dialysis access and insertion site are ipselateral (such as subclavian vein stenosis and occlusion) (130).

Intervention in ESRD patients, particularly for primary prevention of SCD, remains controversial necessitating more studies. Similar to the therapeutic approach of patients with heart failure, intervention should be directed and intensified to well characterised groups of ESRD patients that have been identified as higher risk of VTA and SCD.

6.4.3 ESRD patients at high risk of sudden cardiac death- role of MTWA

A large number of studies have demonstrated strong negative and positive predictive power (similar to invasive electrophysiological testing) of MTWA test results for all cause mortality in ischaemic and non-ischaemic cardiomyopathy (105;106). Based on these initial findings, MTWA was considered an ideal method of identifying those patients with reduced LV function (ejection fraction<30-35%) who would have

survival benefit from primary ICD implantation. Two more recent prospective studies (MASTER and TWA SCD-HeFT) have suggested reduced specificity and sensitivity of MTWA for risk stratifying heart failure patients (109;110). These studies used cardiac arrhythmia, ICD discharge or sudden cardiac death as a composite end point compared to all cause or cardiovascular mortality used in previous studies. Further investigations are currently underway to elucidate the setting in which MTWA would be useful for predicting VTA in heart failure patients and other patients at risk of SCD.

To this end, this study was performed in ESRD patients using MTWA testing to assess the prevalence of and significant associations with an abnormal MTWA result. CMR measurements were obtained in subjects to assess relationship with features of uraemic cardiomyopathy.

These data show that abnormal MTWA test results are common (57.5%) in ESRD patients and this prevalence is similar to previous heart failure studies (236). However, the patients in our cohort had preserved LV function (ejection fraction 61.9±15.3%) suggesting that the aetiology of cardiac arrhythmias differs between ESRD patients and patients with ischaemic and non ischaemic cardiomyopathy. On comparison of these results with diabetics and healthy athletes, abnormal MTWA result was more common in ESRD patients (111).

6.4.4 Comparison between ESRD and hypertensive LVH

Patients with hypertensive LVH and normal renal function were used as controls in this study. Hypertensive LVH differs from uraemic cardiomyopathy both in extent

and pattern of sarcomere expansion and interstitial fibrosis (49;51). This control group was used to provide an indication of the additional risk afforded by uraemic cardiomyopathy and the abnormal myocardial environment in ESRD patients. These data show that prevalence of abnormal MTWA was significantly higher in ESRD patients compared to hypertensive LVH patients despite similar LV size and function between both groups.

An earlier study comparing MTWA results between patients with hypertrophic cardiomyopathy and hypertensive LVH patients found a much higher prevalence of positive test result (31%) in LVH patients compared to data presented in this chapter. However different MTWA exercise protocols (only HR up to 110 bpm were performed) and older classification criteria (indeterminate tests were not reported) were employed in this study (237).

Abnormal MTWA result has been associated with repolarisation alternans, which is defined as discordant and alternating action potential duration between neighbouring cardiomyocytes. Biopsy proven cellular changes (myocyte hypertrophy) and arrangement (disarray) in conjunction with myocardial fibrosis have been associated with abnormal MTWA result and may contribute with repolarisation alternans (103). Endomyocardial biopsies have demonstrated increasing myocardial fibrosis and more heterogeneous histology with worsening CKD (51). One would expect with higher inter-myocyte deposition of collagen (usually type 1), and greater changes in tissue arrangement, there would be greater fluctuations in AP depolarisation/repolarisation, leading to non- uniform depolarisation and increasing risk of abnormal MTWA result and SCD.

However, there are some limitations in this comparison. Prior to recruitment, hypertensive patients were eligible for inclusion based on prior ECG or echocardiographical evidence of LVH. Unfortunately, CMR results showed that only 18 (60%) of patients had LVH using previously defined cut offs for LVMI (154). Furthermore there were no significant differences between myocardial abnormalities of both groups since this study was powered only to determine a difference in MTWA result. On examination of the data, however, ESRD patients had more extreme cardiac abnormalities (represented by higher LVMI, greater variability in LV chamber size, and reduced ejection fraction) and a greater number of cardiovascular risk factors compared to LVH patients.

6.4.5 Implications for an indeterminate MTWA test

The rate of indeterminate tests was high (35.5%) and a large proportion (51%) of these patients were unable to achieve adequate HR elevation reflecting poor exercise tolerance of ESRD patients. A proportion of these patients were able to attempt a repeat test but this did not affect final MTWA result. Poor exercise tolerance in ESRD patients has been demonstrated by other studies and is due to high levels of co-morbidity including peripheral vascular disease, diabetic peripheral neuropathy and pulmonary oedema (238). In heart failure patients, pharmacological attempts to elevate heart rate have been used, however ethical approval for this approach was not obtained. Nonetheless, an indeterminate result has been demonstrated as a significant independent predictor of death (both arrhythmic and non-arrhythmic) in heart failure patients in a small prospective trial (227) and the relevance in ESRD patients remains to be assessed.

6.4.6 MTWA and uraemic cardiomyopathy

This study also demonstrates a strong association between the features of uraemic cardiomyopathy (LVH, LVSD and LV dilatation) and abnormal MTWA result (table 6.3). In patients with other cardiomyopathies (such as dilated or hypertrophic), abnormal MTWA result rate is high (between 65-78%) and it follows that non uniform repolarisation is associated with atypical myocardial cytoarchitecture (e.g. LVH, myocardial fibrosis) (105). Unfortunately, due to the association between gadolinium based contrast agents and nephrogenic systemic fibrosis (NSF), further assessment of myocardial fibrosis could not be performed (239).

6.4.7 Factors associated with abnormal MTWA

ESRD patients with an abnormal test were significantly older, which is similar to findings of previous studies in patients with ischaemic and non ischaemic cardiomyopathy (225). Diabetic patients with ESRD had a significantly higher rate of abnormal test result and this most likely represents the additional, and initially silent, cardiovascular morbidity that diabetics have compared to non-diabetic ESRD patients. In addition, presence of abnormal MTWA result was significantly higher in ESRD patients with history of macrovascular atheromatous disease, namely coronary, peripheral and cerebrovascular, which is reflected in their medical therapy- abnormal result was associated with greater statin usage. Interestingly, there was no difference in aspirin, beta adrenergic blocker and ACE inhibitor or angiotensin receptor blocker therapy between both groups supporting the evidence that these drugs may be under utilised in high cardiovascular risk patients. To further identify factors independently associated with abnormal test, multivariate logistic regression analysis was performed using abnormal MTWA result at the outcome variable. This

confirmed older age, past clinical history of macrovascular diseases, and features of uraemic cardiomyopathy (higher LVMI and presence of LV dilatation) as independent predictors of abnormal MTWA result. Interestingly, abnormal MTWA was independently predicted by clinical history of peripheral and cerebrovascular atheromatous disease. These results suggest that in the absence of CMR evidence of uraemic cardiomyopathy or ischaemic heart disease, interference of cardiomyocyte repolarisation occurs in patients with previous stroke or lower limb vascular insufficiency. It is likely that in these patients, cardiac small vessel disease and clinically silent myocardial ischaemia are present.

At this stage of the study, a trend toward reduced survival in the patients with abnormal MTWA result was demonstrated (Figure 6.3). These results are unsurprising given that major predictors of CV death in ESRD patients include past medical history of CV disease and myocardial structural changes (Chapter 4). Given that abnormal MTWA result was more common in patients with established CV disease, additional information for predicting SCD seems unlikely. However, as more data on patient outcome for this cohort becomes available, the predictive value of MTWA for SCD in ESRD patients can hopefully be fully established.

6.4.8 Limitations of current study

As before this study was limited by the recruitment of patients undergoing pre-transplant CV assessment. Furthermore, although control patients had echocardiographical or ECG evidence of LVH, only 60% had CMR proven LVH. This study was powered to compare differences between MTWA results only based

on pilot data and previously published studies. As a result there was a discrepancy between the numbers of patients in each group.

6.5 CONCLUSIONS

In conclusion, this study demonstrates a strong association between the myocardial abnormalities of uraemic cardiomyopathy and abnormal MTWA result, implicating abnormal ventricular repolarisation with high risk of SCD in ESRD patients. Similarly, a history of macrovascular atheromatous disease is significantly associated with an abnormal MTWA result. The potential role that MWTA may have to independently predict development of cardiac arrhythmia and SCD remains to be assessed.

Chapter 7

A study of ^{31}P Magnetic resonance spectroscopy in uraemic and hypertensive cardiomyopathy

7.1 INTRODUCTION

As discussed in Chapter 1, uraemic cardiomyopathy is characterised by abnormalities of myocardial structure, namely LVH, LVSD and LV dilatation, which are associated with elevated risk of CV morbidity and mortality. In patients with heart failure, abnormal cardiac structure is associated with alteration in cardiomyocyte metabolism (147). Changes occur in metabolic substrate transport and usage, oxidative phosphorylation, and high energy phosphate metabolism. The latter is particularly important since reduced creatine kinase activity results in decreased free ATP concentration, reduced transfer of energy (in the form of high energy phosphate bonds) from cardiomyocyte mitochondria to myofibrils, and elevation of cytoplasmic ADP concentration. ^{31}P-MRS allows non-invasive measurement of relative concentrations of phosphorus containing compounds including ATP, PCr and 2, 3-DPG and thus the assessment of high energy phosphate (HEP) metabolism. Previously, only small studies have been performed in ESRD patients and patients with hypertensive LVH. In addition, the relationships between HEP metabolism and features of uraemic cardiomyopathy have not been investigated.

The aims of this study were to:

- Compare HEP metabolism in a cohort of ESRD patients and hypertensive LVH patients with normal renal function to determine the additional detrimental effects of uraemia.
- Determine associations between uraemic cardiomyopathy and HEP metabolism.

7.2 METHODS

7.2.1 Patients

As before, ESRD patients were recruited from subjects being assessed for renal transplantation as discussed in Chapter 2. In addition, 30 hypertensive patients with ECG or echocardiographic evidence of LVH and normal renal function (within 6 months of recruitment) were assessed (termed LVH patients). Each patient provided cardiovascular history, examination, ECG, and blood for biochemical and haematological profile. Patients with contraindication to MRI (see Chapter 2) were excluded. Since only the effect of uraemia was to be assessed, patients with past or current history of ischaemic heart disease or heart failure were excluded from the study.

7.2.2 CMR acquisition and analyses

CMR scans were acquired for assessment of LV mass and function and analysed as described in Chapter 2. Patients were classified as having LVH, LVSD or LV dilatation based on previously described normal values.

7.2.3 ^{31}P MRS acquisition

Resting ^{31}P MRS was performed in all patients as described in Chapter 2. Care was taken to ensure spectra were acquired from areas of uniform LV contraction (ie not from regions of poor wall motion). Areas under the curve for 2,3-DPG, PCr, and β-ATP were measured, and a blood corrected PCr: βATP ratio (PCr: ATP) calculated (156).

7.2.4 Statistical analyses

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc. Illinois, USA). Data are described as mean± standard deviation. Data were compared by chi squared or Fisher's test for categorical data and paired t-test for continuous data. Correlations between PCr: ATP and cardiac measurements were evaluated by Pearson's and Spearman's correlation coefficient as appropriate.

Twenty anonymised spectra were used for reproducibility studies. Intra-observer variability of PCr: ATP was determined by a single observer (RKP) assessing each scan twice (at least 7 days apart) followed by calculation of the differences between each scan. Inter-observer variability was determined by two independent observers (RKP and T Steedman, Clinical Research Initiative, Western Infirmary, Glasgow) analysing the same scans. The level of difference for PCr: ATP was measured for all scans and the consistency of ratios assessed using the intra-class correlation coefficient (ICC)

7.3 RESULTS

7.3.1 Patient demographics

Clinical, drug and blood data for ESRD (n=53) and LVH (n=30) patients are shown in Table 7.1. Despite excluding patients with symptomatic ischaemic heart disease, there was higher burden of CV disease in ESRD compared to LVH patients; there was a higher number of ESRD patients with a past history of diabetes mellitus, peripheral and cerebrovascular disease, dyslipidaemia, and current or previous history of smoking compared to patients with LVH. Furthermore, use of aspirin, β

blockers, statins and calcium channel blockers was more common in ESRD patients. Diastolic blood pressure was higher in LVH patients compared to ESRD patients probably reflecting wider pulse pressure and increased vascular stiffness in ESRD. There were no significant differences in age, sex, systolic blood pressure and use of warfarin or diuretic therapy between both patient groups. Comparison of blood results between ESRD and a population with normal renal function was as expected (in ESRD patients haemoglobin was lower, inflammatory markers were elevated, biochemical features of secondary hyperparathyroidism were present and serum potassium was higher.) Glucose was also higher in the ESRD compared to LVH patients due to the higher proportion of diabetic patients in this cohort. Serum cholesterol was significantly higher in the LVH group, however the use of statins was lower in these patients compared to ESRD subjects. Brain natriuretic peptide levels were significantly higher in the ESRD group compared to the LVH group, most likely due to chronic fluid overload, myocardial dysfunction and subsequent elevated ventricular wall tension.

7.3.2 Cardiac data

Table 7.2 shows CMR results for ESRD and LVH patients. There were no significant differences in LV systolic function (which was preserved), LV mass or chamber size. Despite echocardiography or ECG evidence of LVH, only 18 (60%) of hypertensive patients had LVH on CMR assessment, based on previously published values. LV systolic dysfunction and dilatation were more common in the ESRD group compared to the LVH group, however, LVSD did not reach statistical significance due to small sample size.

7.3.3 Reproducibility of measurement of cardiac ^{31}P magnetic resonance spectroscopy

To assess reproducibility, twenty anonymised spectra were re-analysed. The intra-observer variability of measurements of PCr: ATP, assessed by absolute difference of ratios was 0.17±0.24, and there was no significance between analyses (p=0.78). The inter-observer variation was determined by comparing mean corrected PCr: ATP for all scans measured by each observer: RKP= 1.28±0.43, TS= 1.21±0.41; p=0.56. Intra-class correlation coefficient was 0.89.

7.3.4 Comparison of ^{31}P-MRS results

Table 7.2 shows comparison of ^{31}P-MRS results between ESRD and LVH patients. There were no significant differences between PCr, β-ATP and 2,3- DPG values. However, mean PCr: ATP ratios (uncorrected and corrected for blood contamination) were significantly lower in ESRD patients compared to LVH patients (corrected PCr: ATP ESRD 1.3±0.5 vs. LVH 1.6±0.4 p=0.007, Figure 7.1). In the ESRD group, there was no significant difference between diabetic and non diabetic patients (PCr: ATP diabetic 1.4±0.7 vs non diabetic 1.3±0.4; p=0.66, data not shown). Only 18 (60%) of hypertensive patients with echocardiographic/ECG evidence of LVH met CMR criteria for LVH. PCr: ATP was significantly lower in ESRD patients compared to hypertensive patients with CMR evidence of LVH (ESRD n=53 corrected PCr: ATP 1.3±0.5 vs. LVH on CMR n=16 :1.7±0.3 p=0.03)

7.3.5 PCr: ATP and uraemic cardiomyopathy

In the ESRD group, PCr: ATP was significantly lower in patients with LV systolic dysfunction (no LVSD 2.0±0.5 vs LVSD 1.2±0.2; p=0.05) and LV dilatation (no LV

dilatation 1.79±0.4 vs LV dilatation 0.98±0.8; p=0.01). LVH was not associated with significant difference in PCr: ATP.

7.3.6 Correlations of PCr: ATP in ESRD patients

There was a weak but significant correlation between corrected PCr: ATP and LV ejection fraction (Pearson's R= 0.31; p=0.03). BSA corrected end systolic volume was negatively correlated with corrected PCr: ATP (Pearson's R= -0.27, p= 0.06), but this did not reach statistical significance (Table 7.3). There were no other significant correlations between PCr: ATP and clinical, blood and cardiac data (including, LVMI, haemoglobin and bone biochemistry).

7.3.7 Determinants of PCr: ATP in ESRD patients

Multivariable linear regression analysis was performed to create the most robust predictive model for PCr: ATP (Table 7.3). Factors considered in the model were those identified as significant (or close) correlates with PCr: ATP. Using backward stepwise regression, the most significant model (highest R^2=0.27) demonstrated LV ejection fraction as the only significant variable that was independently associated with PCr: ATP.

Variable		ESRD N=53	LVH Only N=30	p
Age (years)		54.7(±12.6)	54.6 (±10.6)	0.98
Male (%)		33(63.3)	24 (80.0)	0.09
BMI (kg/m^2)		26.2(±5.2)	27.1(±3.6)	0.41
Systolic BP (mmHg)		142 (±23)	139 (±17)	0.53
Diastolic BP (mmHg)		81 (±14)	87 (±9)	0.03
RRT	HD	37 (69.8)	-	
	PD	0	-	
	CKD 5	16(30.2)	-	
RRT Time(years)		1.26 (1.9)	-	
Primary Renal Disease				
	Diabetic Nephropathy	22 (41.5)	-	
	APCKD	5(9.4)	-	
	Glomerulonephritis	6(11.3)	-	
	Renovascular Disease	4(7.5)	-	
	Chronic Pyelonephritis	5(9.4)	-	
	Other/Uknown	11(20.8)	-	
Diabetes mellitus		14 (26.4)	0	<0.01
Hypertension		39 (73.6)	30 (100)	0.08
Cerebrovascular disease		11 (20.8)	1 (3.3)	
Peripheral vascular disease		12 (14.5)	0	
Dyslipidaemia		25 (47.1)	9(30)	<0.01
Smoking	Never	22 (41.5)	19 (63.3)	0.06
	Current	17 (32.1)	3(10)	
	Ex	14 (26.4)	8 (26.7)	
Epo receptor Agonist		46(86.8)	0	
β Adrenoceptor Blocker		25 (47.2)	10 (33.3)	<0.01
Aspirin		35 (66.0)	3 (10)	<0.01
Warfarin		3(5.7)	0	0.63
Clopidogrel		3(5.7)	0	
ACEI/ARB		30 (56.6)	12 (40.0)	0.08
Diuretic		13(24.5)	6 (20.0)	0.11
Nitrate		0	8(26.7)	
Calcium Channel Blocker		26 (49.1)	8(26.7)	0.02
α Adrenoceptor Blocker		6 (11.3)	1 (3.3)	
Statin		30 (56.6)	9(30.0)	0.03
Haemoglobin (g/dL)		11.8(±2.2)	14.8(±1.4)	<0.01
Fibrinogen (g/L)		4.1(±1.0)	3.2(±0.5)	<0.01
ESR (mm/s)		29 (14, 56)	8(2, 10)	<0.01
CRP (mg/L)		5.0(3.3, 13.3)	1.1 (0.7, 4.3)	<0.01
Adjusted Ca^{2+}(mmol/L)		2.33(±0.2)	2.41 (±0.1)	<0.01
PO_4 (mmol/L)		1.52(±0.4)	1.05 (±0.1)	<0.01
PTH (pmol/L)		19.3(11.6, 45.1)	5.6(4.6, 7.5)	<0.01
Glucose (mmol/L)		9.1(±1.8)	5.2(±3.3)	<0.01
HbA1c (%)		6.9(±2.8)	5.4(±0.9)	0.02
Potassium (mmol/L)		4.8(±0.3)	4.1(±0.3)	<0.01
BNP (ng/L)		228(134, 557)	27 (13, 43)	<0.01
Cholesterol (mmol/L)		4.3(±1.2)	5.4(±1.2)	<0.01
Triglyceride (mmol/L)		1.9(±0.8)	2.0(±1.1)	0.68
HDL- Chol (mmol/L)		1.2(±0.6)	1.4(±0.4)	0.14
LDL- Chol (mmol/L)		2.4(±0.4)	2.8(±0.8)	0.21

Table 7.1 Comparisons of clinical and blood results between ESRD and LVH patients.

Data are number with percentage in parentheses and mean ± standard deviation except for ESR, CRP, PTH and BNP where median and interquartiles are shown.

Variable	ESRD N=53	LVH Only N=30	P
Ejection Fraction (%)	**66.4(±12.4)**	**65.5(±11.2)**	**0.75**
Myocardial mass/BSA	**87.5(±30.4)**	**82.4(±32.6)**	**0.48**
EDV/BSA (ml/ m^2)	**63.8(±24.9)**	**65.7(±14.1)**	**0.70**
ESV/BSA (ml/ m^2)	**22.4(±15.8)**	**23.2(±12.1)**	**0.81**
LVH on MRI	**33(62.2)**	**18 (60)**	**0.72**
LVSD on MRI (EF<55%)	**8(22.9)**	**1(3.3)**	**0.07**
LV dilatation	**22 (41.5)**	**1(3.3)**	**<0.01**
PCr	**7.7(±3.8)**	**8.3(±3.6)**	**0.48**
β-ATP	**6.5(±3.1)**	**5.3(±2.6)**	**0.10**
2,3-DPG	**1.1(±0.8)**	**1.2(±0.9)**	**0.55**
Uncorrected PCr: βATP	**1.9(±0.8)**	**2.4(±0.7)**	**<0.01**
Corrected PCr: βATP	**1.3(±0.5)**	**1.6(±0.4)**	**<0.01**

Table 7.2 Comparisons of cardiac and 31P MRS results between ESRD and LVH patients.

Data are number with percentage in parentheses and mean ± standard deviation.

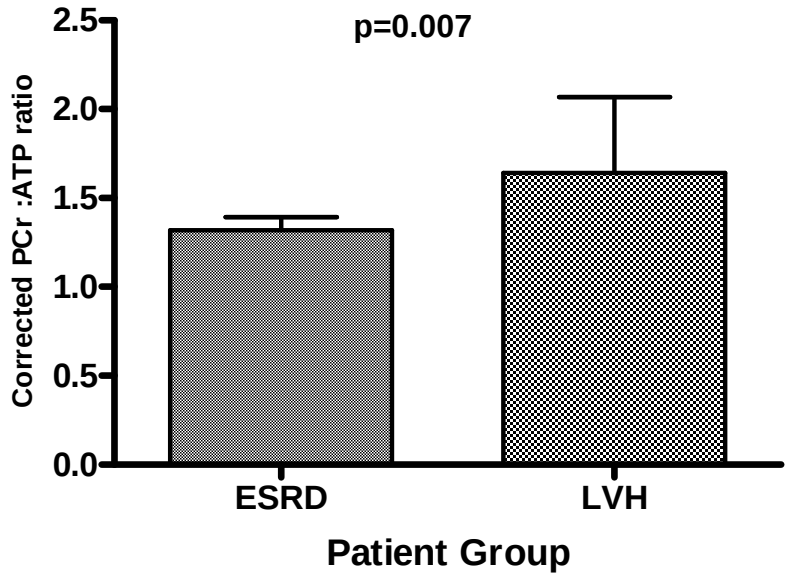


Figure 7.1 Bar chart showing mean (± standard deviation) of corrected PCr: ATP for ESRD (n=53) and LVH patients (n=30)

					p	95% CI
			Constant 0.35		0.27	-0.28-0.98
	r	p	B	β		β
LV Ejection fraction (per %)	0.31	0.03	0.10	0.27	0.04	0.21-0.42
ESV/BSA (per ml/m^2)	-0.27	0.06				
LDL- Cholesterol (per mmol/l)	0.35	0.20				
Serum Cholesterol (per mmol/l)	0.30	0.24				
ESR (per mm/s)	0.59	0.07				
Male Sex	-0.17	0.22				
BMI (per kg/m^2)	-0.05	0.75				
Haemodialysis (ref predialysis)	0.08	0.54				
Systolic Blood Pressure (per mmHg)	0.06	0.66				
Diastolic Blood Pressure (per mmHg)	0.16	0.25				
Haemoglobin (per g/dL)	0.15	0.56				
Fibrinogen (per g/L)	-0.36	0.20				
CRP (per mg/L)	0.02	0.94				
Serum Calcium (per mmol/l)	0.21	0.88				
Serum Phosphate (per mmol/l)	-0.43	0.86				
Ca x PO4 Product(per mmol^2/l^2)	-0.12	0.93				
Parathyroid Hormone (per pmol/l)	-0.06	0.66				
Glucose (per mmol/l)	-0.21	0.17				
Serum Potassium (per mmol/l)	-0.05	0.74				
Triglyceride (per mmom/l)	0.25	0.11				
HDL- Cholesterol (per mmol/l)	0.09	0.55				
BNP (ng/L)	-0.33	0.13				
LVMI (per g/m^2)	-0.96	0.34				
EDV/BSA (per ml/m^2)	-0.08	0.56				
Diabetes Mellitus	0.03	0.81				
Cerebrovascular Disease	-0.05	0.74				
Peripheral vascular disease	-0.03	0.82				
Smoker	0.04	0.79				
B Blocker	0.08	0.58				
Aspirin	-0.05	0.72				
Erythropoietin	-0.27	0.16				
ACE Inhibitor/ARB	0.15	0.21				
Calcium Channel Antagonist	0.18	0.16				
Statin	-0.13	0.33				

Table 7.3 Correlation between PCr:ATP and clinical, blood and cardiac parameter (left) and multivariate linear regression (right) entering only significant correlates into the (backward stepwise) model (adjusted R^2=0.27).

7.4 DISCUSSION

^{31}Phosphorus magnetic resonance spectroscopy has been used *in vivo* to study LV high energy phosphate (HEP) metabolism in human hearts (145;146). As stated in Chapter 1, inherited and acquired cardiomyopathies are not only associated with abnormal cardiac structure but also reduced PCr: ATP in areas of apparently normal LV contraction. These results suggest that although echocardiography or CMR may demonstrate "normal" myocardial contraction, biochemical abnormalities are present which may precede development of systolic dysfunction by reducing metabolic activity and/or efficiency (147). The clinical relevance of HEP metabolism has been demonstrated in heart failure patients, where reduced myocardial PCr: ATP has been significantly associated with lower LVEF and NYHA symptom severity. Furthermore, in dilated cardiomyopathy patients, lower PCr: ATP is significantly associated with reduced survival and is a better predictor of survival than LVEF or NYHA class (144).

As shown in Chapter 4, features of uraemic cardiomyopathy are associated with poorer survival and are independent predictors of adverse CV outcome. In ESRD patients, presence of wall motion abnormalities are rare at rest (240), indicating that global, uniform LV "disease" is a more common cause of reduced LV ejection fraction.

In this current study, HEP metabolism was investigated in a cohort of ESRD patients. Patients with known ischaemic heart disease were excluded to assess the effect of uraemia and small vessel ischaemia (Table 8.1). Acquisition voxels were

placed on visibly functioning myocardium to ensure that PCr: ATP was measured from viable cardiac tissue and not scar/fibrotic tissue. As a control group, patients with LVH due to hypertension were assessed to allow the effect of additional abnormalities (LVSD and LV dilatation) and uraemia to be determined in ESRD patients.

7.4.1 Reduced PCr:ATP in uraemic cardiomyopathy

The biochemical changes that accompany reduced PCr:ATP are not completely understood and derived mostly from animal studies. Lowered PCr:ATP indicates that in the resting state there are reduced myocardial energy reserves and in animal models for cardiac hypertrophy (e.g. spontaneously hypertensive rat) a reduction in PCr:ATP has been demonstrated (241;242). In clinical and experimental models of cardiac failure, reduced PCr:ATP ratio have been attributed to reduced levels of creatine kinase activity. However, in animal models of uraemic cardiomyopathy changes in creatine kinase activity (243) and cyptoplasmic creatine concentration have not been convincingly demonstrated (244).

Impaired ATP synthesis (e.g. from oxidative phosphorylation) or increased utilisation (excitation- contraction coupling) may reduce PCr by the buffering creatine kinase system. Furthermore, the subsequent elevation in free cyptoplasmic ADP may affect cardiac function adversely, since high ADP concentration inhibit myosin ATPase activity thus exacerbating contractile dysfunction. These experimental finding are consistent with the results of this study. In ESRD patients, not only were features of uraemic cardiomyopathy (LVSD and LV dilatation),

significantly associated with reduced PCr:ATP ratio but LV ejection fraction was the only variable that was independently associated with PCr:ATP measurements.

7.4.2 Comparison of PCr: ATP result

The values obtained for ESRD and LVH patients are comparable to previous studies (149;245). These results show that despite similar LV mass, function and chamber size, PCr: ATP ratios were significantly lower in ESRD patients compared to LVH patients. As one would expect, there were significantly more ESRD patients with LVSD and LV dilatation using established criteria. Only 60% of hypertensive patients with LVH on echocardiography had evidence on CMR, highlighting greater accuracy of LV mass measurement using CMR. PCr:ATP ratio was similarly lower in ESRD patients compared to hypertensive patients with LVH on CMR. Consistent with a previous smaller study which compared HEP metabolism between diabetic and non diabetic uraemic patients (149), there was no significant difference in PCr: ATP between diabetic and non diabetic ESRD patients.

The differences between PCr:ATP in ESRD and LVH patients are most likely due to alteration of:

- Composition of myocardial interstitial tissue
- Cardiomyocte metabolic function.

7.4.3 Alteration in intercellular composition- myocardial fibrosis.

Left ventricular hypertrophy is characterised by changes in tissue architecture including myocardial fibrosis and expansion of sacrcomere volume and density. In patients with systemic hypertension and ESRD, myocardial fibrosis is a consequence of accumulation of collagen, mostly type 1 fibres, within the cardiac interstitium, and around the intermyocyte arterial tree. This accumulation is due to a combination of excessive collagen production by fibroblasts accompanied with reduced or unstable degradation of older fibres by extracellular metalloproteinases (50; 51).

Initially in patients with hypertension and CKD, factors such as pressure overload, oxidative stress, inflammation and production of pro- fibrotic cytokines (namely TGF-β and cardiotrophin-1) stimulate collagen fibre production. Both in vitro and in vivo studies using the spontaneously hypertensive rat (SHR), have demonstrated that chronic pressure overload stimulates procollagen gene expression and collagen protein synthesis resulting in deposition of collagen fibres within the cardiac interstitium (51). Post-mortem and endomyocardial biopsy studies of hypertensive and ESRD patients have demonstrated similar patterns of collagen deposition reflecting lines of excessive wall stress and increasing collagen density proportional to wall thickness (246;247). Angiotensin II is a potent stimulator of cardiac fibrosis in humans with hypertension via stimulation of the angiotensin II receptor- 1 and is facilitated by locally produced factors produced by cardiomyocytes (e.g. ostepontin, endothelin-1). Studies assessing regression of fibrosis using ACE inhibitors or AII receptor blockers have demonstrated some improvement in patients with no renal impairment but little effect in ESRD individuals (248;249).

Myocardial fibrosis is also stimulated by other factors in advanced stages of renal disease. Parathyroid hormone stimulates rat cardiac fibroblast proliferation in vitro. In 5/6 nephrectomised rats (acting as an animal model of uraemic cardiomyopathy), interstitial fibroblasts express higher levels of proliferation markers (eg proliferating cell nuclear antigen), platelet derived growth factor, integrin β1 and laminin compared to experimental models of genetic hypertension (61;250).

In patients with hypertensive heart disease, the degree of myocardial fibrosis has previously been assessed using endomyocardial biopsy, MRI with gadolinium enhancement, and serum markers for collagen type 1 deposition (251). In patients with advancing stages of CKD, the degree of LVH and indicators of diastolic dysfunction increase at a similar rate and this may be due, in part, to higher levels of myocardial fibrosis. Patients with worsening degrees of CKD have consistently demonstrated higher levels of inter-myocyte fibrosis (252). Furthermore, in patients with dilated cardiomyopathy, dialysed patients have been shown to have more severe and disorganised myocardial fibrosis on endomyocardial biopsies compared to their non dialysed counterparts (253). Taken together, interstitial cardiac fibrosis is likely to contribute to CMR and echocardiographical features of uraemic cardiomyopathy.

Thus it is likely that a greater degree of inter-myocyte fibrosis within the tissue of interest is a significant contributing factor to reduced PCr:ATP ratio in ESRD patients compared to LVH ones. Reduction of measured HEP metabolism may be a consequence of:

- Impeded nutrient/metabolic substrate (e.g. glucose, oxygen) transfer to cardiac myocytes as a result of intervening collagen.

- Reduced cardiomyocyte volume per acquisition voxel due to presence of fibrosis which may not interfere with macroscopic contracting tissue.

7.4.4 Alteration of cardiomyocyte function

Several animal model and clinical studies have demonstrated abnormalities of cardiomyocyte metabolism in uraemia.

7.4.4a Abnormal cyptoplasmic calcium cycling within cardiomyocytes.

Since intracellular Ca^{2+} plays a central role in excitation-contraction coupling of cardiomyocytes, alterations of intracellular handling may contribute to contractile failure. In experimental rat models of uraemic cardiomyopathy (5/6 nephrectomy), elevating extracellular perfusing Ca^{2+} did not have an effect on uraemic hearts (n=8) compared to the positively inotropic response of sham operated controls (n=8), despite similar changes in heart rate (244). This was also associated with a reduced PCr:ATP in the uraemic cardiomyopathy group compared to controls. The authors concluded that disordered myocardial calcium usage may contribute to cardiac metabolic derangements. Furthermore, the same group performed isolated ventricular myocyte studies from similar rat groups. Using steady state field stimulation to investigate intracellular Ca^{2+} concentration changes during cell contraction, significant slowing of return to diastolic intracellular Ca^{2+} levels compared to controls was demonstrated in myocytes from uraemic hearts (254). This effect has been abolished by inhibiting the Na^{+}/Ca^{2+} exchanger suggesting that membrane bound transporters play a pivotal role in controlling intracellular Ca^{2+} concentrations and relaxation during diastole in myocytes from uraemic hearts (255).

Similarly, in an isolated rat cardiac myocyte system investigating Ca^{2+} cycling and contractile function, treatment of these cells with uraemic patient sera (n=6) resulted in prolongation of cell relaxation and calcium mediated recovery compared to sera from healthy controls (256). Thus, uraemia is associated with abnormal Ca^{2+} cycling which may significantly affect excitation coupling and relaxation of cardiac tissue and utilisation of ATP during the cardiac cycle.

7.4.4b Microvascular disease and myocardial ischaemia

Development of cardiac hypertrophy is commonly due to an adaptive response to pressure and volume overload. However, a mismatch of energy demand (from hypertrophied myocytes) and supply (due to inadequate angiogenesis) may contribute to the development of cardiac failure (257).

Myocardial ATP production is primarily achieved by oxidative phosphorylation and the creatine kinase reaction acts as a cardiac energy buffer/reserve providing ATP rapidly to the sites of need. Cardiomyocyte ATP production is directly related to myocardial oxygen consumption, and any reduction in oxygen supply has a profound effect on cardiac energetics and the PCr:ATP ratio. In this study, there was no significant difference in cardiac parameters between ESRD and LVH groups even when patients with symptomatic CAD were excluded. Furthermore, care was taken not to acquire spectra from areas of obvious wall motion abnormality. Nonetheless, it is likely that microvascular disease due to inadequate angiogenesis, myocardial ischaemia and subsequent reduction of mitochondrial oxidative phosphorylation may be an important cause of reduced PCr:ATP ratio in uraemic hearts. As stated before,

silent myocardial ischaemia is common in ESRD patients and often associated with CMR features of LVSD (139).

The cause of inadequate angiogenesis in ESRD is not due to hypertension alone and appears to be specific to the heart. In 5/6 nephrectomised rats, the density of cardiac capillaries is less than sham operated controls and the SHR model for hypertension (258). Similarly studies have shown lower cardiac capillary density in uraemic patients compared to subjects with LVH due to hypertension and healthy controls (257). However, this inadequate angiogenesis was not found in other muscles (e.g. psoas). The cause of this uraemia specific effect is not clear but may be related to centrally acting sympathetic stimulation and locally derived endothelial factors since in experimental models, cardiac capillary density could be improved by monoxidine and endothelin receptor blockers (49;257;259). These effects could not be reproduced with calcium channel blocking agents or ACE inhibitors.

Other alterations of cardiac metabolism occur during low oxygen supply. Changes in metabolic substrate usage of cardiomyocytes from fatty acids to glucose have been described in hypoxic conditions. Interestingly, experimental rat models of uraemic cardiomyopathy have demonstrated reduction in expression of membrane glucose transporter, Glut 4, possibly further hindering substrate availability for oxidative phosphorylation (49).

7.4.5 Limitations of current studies

This small study was limited by noisy signal during MRS acquisition. This was minimised by ensuring the magnetic field was homogenised completely. As before, only 60% of patients labelled as "LVH" had evidence on CMR. However this did not alter the findings that cardiac energy metabolism was lower in ESRD patients and patients with LVH when CMR confirmed cases were compared. An interesting additional control group would have been healthy individuals, however ethical approval was not obtained for this part of the study.

7.5 CONCLUSIONS

This study shows that despite similar myocardial mass, ESRD patients have lower HEP metabolism compared to LVH patients. This may be due to greater myocardial fibrosis or altered myocyte metabolic function in ESRD patients. Lower PCr: βATP ratio is associated with features of uraemic cardiomyopathy

Chapter 8

A study of changes in left ventricular mass after renal transplantation

8.1 INTRODUCTION

As discussed in Chapter 1, left ventricular hypertrophy (LVH) is the most common myocardial abnormality in patients with ESRD, a component of uraemic cardiomyopathy, and an independent risk factor for sudden cardiac death, heart failure, and cardiac arrhythmias in the general population and dialysis patients (1;205). Furthermore, successful renal transplantation (RT) is associated with lower cardiovascular morbidity and mortality compared to patients who remain on the transplant waiting list (201;202) and has been associated with significant echocardiographic regression of LVH (260;261).

The inaccuracies of echocardiographic estimation of left ventricular mass (LV mass) in patients with ESRD, as previously discussed, are due to geometric assumptions made during calculation of LV mass and limited visualisation of chamber borders. To this end, cardiac magnetic resonance (CMR) imaging has been used to provide a more detailed, volume independent, measurement of cardiac structure in this patient population.

The aim of this study was to compare changes in LV structure and function between patients who undergo RT and those who remain on the transplant waiting list receiving maintenance haemodialysis (HD).

8.2 METHODS

8.2.1 Patients

The subjects from this study were obtained from a larger project investigating outcomes in patients undergoing cardiovascular assessment for renal transplantation. Patients were recruited from the renal transplant assessment clinic from the Western Infirmary as described in Chapter 2. This study recruited 25 patients accepted onto the transplant waiting list who were later successfully transplanted (defined as serum creatinine <150 µmol/litre at the time of second scanning), and another 25 patients accepted for transplantation, who remained on the waiting list.

8.2.2 CMR acquisition

Initial CMR scans were acquired as part of assessment of LV function and analysed as previously described. Patients were invited for repeat CMR scan as part of the study. Definitions of LVH, LVSD and LV dilatation have been presented in Chapter 2.

8.2.3 Data collection

Mean haemoglobin and blood pressures were calculated from monthly measurements 3 months before and after CMR scanning. Blood pressure measurements taken immediately before the start of haemodialysis were recorded.

8.2.8 Statistical analyses

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc. Illinois, USA). Data are expressed as mean ± standard deviation or median and interquartile

range. Comparisons were made between those patients who received a transplant and those who remained on the waiting list by student's t test (for normal data) or Mann-Whitney U test (for non-normal data). Time between scans for both groups was calculated from the difference between dates of CMRs. Due to inter-patient variation in time between CMR scans, changes were expressed as percentage change per year (%/y).

8.3 RESULTS

8.3.1 Patient demographics

Fifty patients were studied. The mean time between the CMR studies was 2.8±1.1 years for those patients who were transplanted and 2.4 ±1.2years for those remaining on the waiting list. No patients had cardiac events (myocardial infarction, acute coronary syndrome, cardiac arrhythmias) between scans.

The demographic data are presented in Table 8.1. This shows that patients who received a transplant were younger at the time of first scan (45.9± 14.4 years vs 52.7 ± 10.4 years; p=0.06) compared to those who remained on the transplant waiting list. However, there was no significant difference in the number of patients who were male, who had diabetes mellitus, a past history of ischaemic heart disease, hypertension, heart failure, or in the smoking status (although there was a trend towards non-smokers in the transplanted group). At the time of first scan, there was no significant difference in duration on renal replacement therapy between both groups (not transplanted 2.3±2.6 years vs. transplanted 3.0±3.0years; p=0.47). The distribution of cardio active drugs was not significantly different between the groups.

The only noted change was that one patient was on erythropoietin following transplantation, compared to 80% of those who remained on the waiting list. All transplant recipients were receiving low dose maintenance glucocorticoid therapy, a purine synthesis inhibitor, and a calcineurin inhibitor as part of their immunosuppressive regimen.

Systolic blood pressure was higher after transplantation and during transplant assessment (performed on a non-dialysis day). However, there was no significant difference in systolic or diastolic blood pressure between those transplanted or those remaining on the waiting list; nor was there a change in the number of anti-hypertensive agents taken. Haemoglobin was well controlled on dialysis, and there was no significant difference between groups after transplantation.

8.3.2 Cardiac structure and function

Table 8.2 shows cardiac measurements for both CMR scans. There was no difference in any of the cardiac parameters measured (Table 8.2) – ejection fraction, left ventricular mass index (Figure 8.1), BSA corrected end-diastolic and end-systolic volumes before transplantation or on follow-up scans.

There was a small reduction in left ventricular mass index (-3.6% per annum) in dialysis patients and a small increase associated with transplantation (+2.8% per annum). However, none of the measured cardiac parameters achieved statistical significance (Figure 8.1). The proportion of patients with left ventricular hypertrophy was 68% in both groups and did not change significantly on follow-up.

		Not Transplanted N=25	Transplanted N=25	p
Age		**52.7 (±10.4)**	**45.9(±14.4)**	**0.06**
Male		**15 (62.5)**	**20 (80)**	**0.18**
Diabetes Mellitus		**4 (16)**	**5(20)**	**0.11**
Past history IHD		**6 (24)**	**4(16)**	**0.48**
Hypertension		**24 (96)**	**22 (88)**	**0.29**
Heart Failure		**3 (12)**	**1(4)**	**0.29**
Smoking status				
Never		**8 (32)**	**16(64)**	
Yes		**11 (44)**	**6(24)**	**0.08**
Ex		**6(24)**	**3(12)**	
Number on haemodialysis		**12(48)**	**10 (44)**	**0.41**
Time on RRT prior to CMR1(y)		**2.31 (±2.6)**	**3.01(±3.0)**	**0.47**
Drug History				
ESA	**CMR 1**	**20(80)**	**18 (72)**	**0.51**
	CMR 2	**20 (80)**	**1 (4)**	**<0.01**
Beta Blocker	**CMR1**	**8(32)**	**11(44)**	**0.38**
	CMR2	**19(76)**	**15(60)**	
Aspirin	**CMR1**	**6(24)**	**9(36)**	**0.36**
	CMR2	**10 (40)**	**9(36)**	**0.77**
ACE-I/AIIRA	**CMR1**	**7 (28)**	**6(26)**	**0.75**
	CMR2	**8(32)**	**9(36)**	**0.77**
Calcium channel antagonist	**CMR1**	**2 (8)**	**7 (28)**	**0.06**
	CMR2	**4 (16)**	**6(24)**	**0.48**
Other clinical data				
Mean SBP	**CMR1**	**139 (±17.2)**	**135 (±20.1)**	**0.40**
	CMR2	**145 (±20.5)**	**147(±17.4)**	**0.31**
Mean DBP	**CMR1**	**81 (±12.3)**	**78(±11.5)**	**0.41**
	CMR2	**77 (±13.2)**	**81(±13.1)**	**0.35**
Mean BMI (kg/m^2)	**CMR1**	**26.4(±4.0)**	**26.1(±5.2)**	**0.79**
	CMR2	**26.8 (±4.1)**	**27.0(±5.7)**	**0.92**
Mean Hb (g/dL)	**CMR1**	**12.1 (±1.8)**	**11.9(±1.9)**	**0.61**
	CMR2	**13.0 (±7.0)**	**12.8 (±2.3)**	**0.89**
Mean Haematocrit	**CMR1**	**0.38 (±0.05)**	**0.37(±0.06)**	**0.22**
	CMR2	**0.37(±0.05)**	**0.39(±0.06)**	**0.26**

Table 8.1 Comparison of demographic, clinical and drug data for patients.

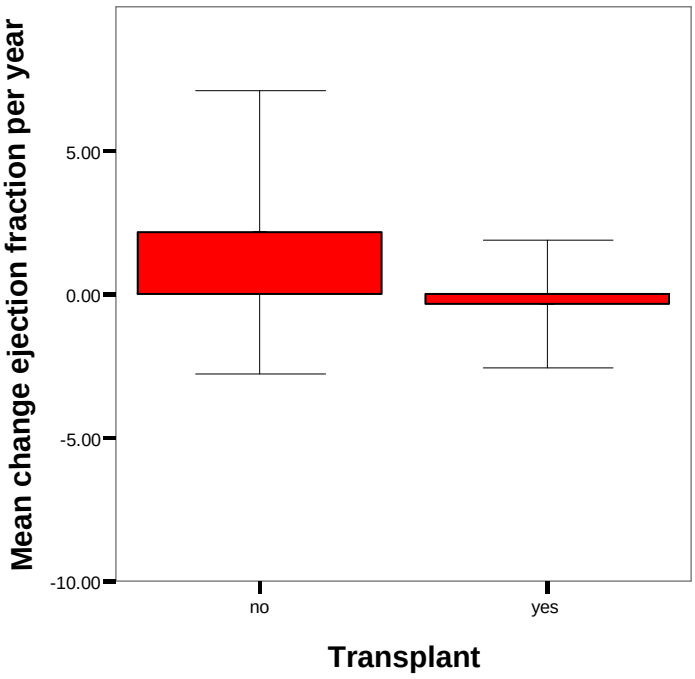
CMR1= first CMR; CMR2= second CMR. Data are number with percentage in parentheses or mean ± standard deviation

		Not Transplanted N=25	Transplanted N=25	p
Mean Time between CMRs (y)		**2.4(±1.1)**	**2.8 (±1.2)**	**0.14**
Mean Time Transplant to CMR2 (y)			**1.8 (±0.9)**	
Ejection Fraction %	**CMR1**	**64.2 (±12.2)**	**66.3(±11.5)**	**0.56**
	CMR2	**64.7 (±11.5)**	**67.1 (±12.2)**	**0.52**
LVMI (g/m^2)	**CMR1**	**90.5 (75.1, 113.5)**	**94.7 (77.2, 108.7)**	**0.96**
	CMR2	**87.4 (69.3, 112.1)**	**99.1 (79.1, 119.9)**	**0.27**
EDV/BSA (ml/ m^2)	**CMR1**	**74.6(±31.4)**	**69.3(±18.9)**	**0.51**
	CMR2	**59.2 (±18.9)**	**62.3 (±18.6)**	**0.59**
ESV/BSA (ml/ m^2)	**CMR1**	**28.8 (±23.3)**	**24.3±(±20.6)**	**0.55**
	CMR2	**21.9(±17.4)**	**25.4(±20.7)**	**0.51**
% change ejection fraction/year		**+ 2.1 (±11.9)**	**- 0.4 (±5.3)**	**0.34**
% change LVMI/year		**- 3.6 (±16.7)**	**+ 2.8 (9.1)**	**0.10**
% change EDV/year		**- 3.4 (±31.5)**	**+ 0.1(±19.5)**	**0.64**
% change ESV/year		**+ 3.0 (±55.5)**	**+ 15.2 (±65.2)**	**0.48**
LVH	**CMR1**	**17 (68)**	**17 (68)**	**1.00**
	CMR2	**15 (60)**	**19 (76)**	**0.23**
LVSD	**CMR1**	**5 (20)**	**3(12)**	
	CMR2	**2 (8)**	**2 (8)**	
LV dilatation	**CMR1**	**5(20)**	**4 (16)**	
	CMR2	**1 (4)**	**0**	

Table 8.2 Comparisons of cardiac MRI results for baseline (CMR1) and second scan (CMR2).

Data are mean ± standard deviation in parentheses except for LVMI on MRI where median and interquartile range is shown**.**

(a)



(b)

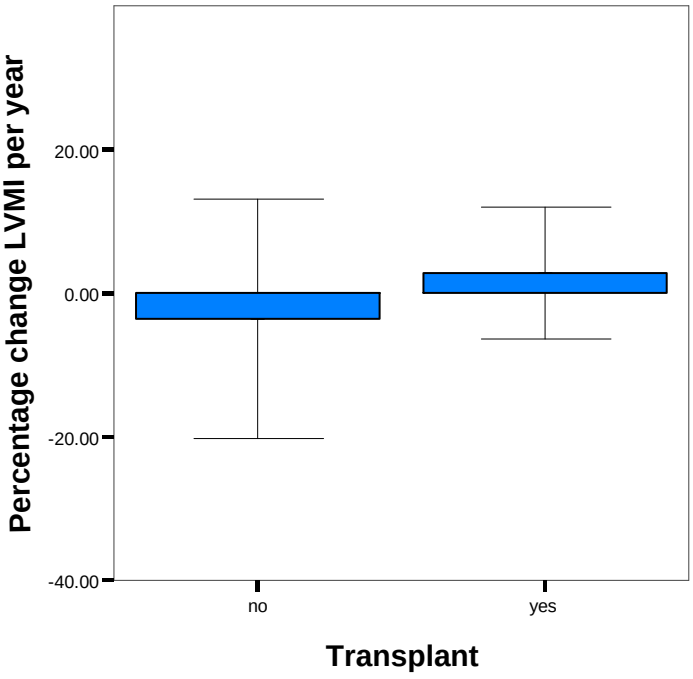


Figure 8.1 Bar graphs demonstrating (a) mean percentage change of ejection fraction per year (with 95% confidence intervals; p=0.34). (b) mean percentage change of LVMI per year (with 95% CI; p=0.10)

8.4 DISCUSSION

The incidence of patients commencing renal replacement therapy is increasing (262). Renal transplantation remains the treatment of choice for patients with ESRD due to improved morbidity and significant increase in life expectancy. This has been shown in a number of studies:

- In a longitudinal study comparing survival between transplanted and wait-listed patients between 1991 and 1997, Wolfe et al demonstrated an increased risk of death in the immediate 2 weeks following transplantation (RR 2.88). However, there was a significant reduction in mortality after 18 months (RR 0.32, 95% CI 0.30-0.35, $p<0.01$) in transplant recipients compared to patients that remained on the renal transplant waiting list (201).
- A study conducted in Scotland, assessed survival in first renal transplant recipients and demonstrated a long term reduction in the risk of death after 18 months (RR 0.18 95% CI 0.08-0.82) compared to patients on dialysis. Projected life expectancy for transplant recipients was significantly higher (17.19 years transplant vs. 5.88 years on dialysis) (263).

Improved survival is believed to be due to a number of factors including improvements in immunosuppression, organ procurement, patient selection and preparation, and surgical techniques. However, cardiovascular death is very common in patients with functioning renal transplants and although renal transplantation confers a favourable cardiovascular survival benefit this is still 50-fold higher than the general population:

- In a retrospective analysis from the United States Renal Database Service, Meier-Kriesche et al demonstrated a significant improvement in long term cardiovascular survival in 60 181 first kidney transplant recipients compared to patients that remained on the renal transplant waiting list. CV death rates decreased as transplant vintage increased and this relationship existed for living and deceased donor transplants (202).

This cardiovascular benefit is unexpected due to the deleterious effect of renal transplantation on established cardiovascular risk factors including immunosuppression related hypertension, dyslipidaemia, anaemia and diabetes mellitus (262). Some investigators believe that renal transplantation may have an effect on uraemic cardiomyopathy, specifically regression of LVH.

8.4.1 Renal transplantation and cardiac structure

Given the close relationship between cardiomyopathy, long standing renal disease, and cardiovascular survival it has been postulated that improved renal function and better fluid volume control after renal transplantation may reverse or alleviate abnormalities of uraemic cardiomyopathy.

Most studies have been performed in patients with pre-existing cardiac disease before transplantation:

- Melchor et al prospectively investigated the effect of renal transplantation in 29 recipients with echocardiographic evidence of LV dysfunction. They demonstrated significant improvement in LVEF (pre transplant EF= 38.8%, post transplant EF=

58.2%; p<0.001) with a reduction in LVH prevalence (21% pre transplant to 18% post transplant) (264).

- Wali et al investigated 138 patients with CKD 5, LV dysfunction (EF≤ 40%) and symptomatic chronic heart failure. Repeat radionuclide ventriculograms performed at 6 and 12 months post transplant demonstrated improved mean LVEF (32 to 52%) which was associated with improvement in NYHA classification and lower mortality and hospitalisation (265).
- Midvetdt et al demonstrated 15% reduction in LVMI after renal transplantation using echocardiography in a study comparing nifedipine and lisinopril to control blood pressure in hypertensive transplant recipients. (266).

However in patients with LVH only, the effect of renal transplantation on cardiac structure remains controversial:

- Peteiro et al examined 30 patients before and after (10±1.8 months) renal transplantation using M-mode echocardiography. These patients had near normal LV ejection fraction. They demonstrated a significant reduction in ESV, EDV and LVMI (201g/m^2 pre transplant to 171g/m^2 post transplant; p<0.01) but no significant change on LVEF (200).
- Ferriera et al demonstrated a significant decrease in LVMI and LV dilatation after renal transplantation. There was resolution of LVSD (8.3% of patients before transplantation to none after) but overall LVEF did not increase significantly (52.9% pre transplant to 60.0% 12 months post transplant; p=0.88) (267).

CMR scanning provides a more detailed characterisation of the left ventricular borders resulting in consistently reproducible measurements compared to echocardiography (Chapter 1). In view of this, the present study was performed using CMR to provide accurate, volume independent assessment of LV mass. There was no significant change in left ventricular mass index between patients who were receiving hospital haemodialysis for a period of 2-3 years and patients who underwent successful transplantation over the same time scale. Similarly, there was no difference in LV chamber volumes or ejection fraction between the groups.

8.4.2 Left ventricular mass after renal transplantation

These findings cast doubt on the reversibility of left ventricular hypertrophy after renal transplantation. As described in chapter 3, the main determinants of LV mass in haemodialysis patients are elevated cardiac preload (volume overload) and afterload (systemic hypertension and markers of vascular calcification). These data suggest that some of these features persist after renal transplantation perpetuating development and/or preventing reversal of LVH.

8.4.2(a) Hypertension

Hypertension is the most common cardiovascular risk factor in transplant recipients and is significantly associated with adverse outcome:

- Recent observational studies have demonstrated significant association between mortality and blood pressure in renal transplant recipients. In the largest study to date, Kasiske et al demonstrated that a 10mm Hg increase in systolic BP was associated with an increase in death (RR 1,18 95% CI 1.12, 1.23), and total or death censored graft failure (268).

The most potent aetiological factors for post transplant hypertension are pre transplant hypertension and use of calcineurin inhibitors (260;262). In this cohort, there was no significant reduction in BP after renal transplantation (Table 8.1) and all transplant recipients were immunosuppressed with either tacrolimus or cyclosporine. Together, these findings suggest that hypertension may be associated with increase in LVMI after renal transplantation.

8.4.2(b) Bone mineral disorders

The relationship in haemodialysis patients between LVMI and abnormal bone mineral metabolism (Chapters 1 and 3) has previously been discussed. Although much has been published in dialysis population, there is a paucity of studies investigating the effect of correcting bone mineral parameters after renal transplantation. No data was obtained data regarding calcium and phosphate for this study.

8.4.2 (c) Fluid overload

One of the benefits of successful renal transplantation is a return to near normal body electrolyte and thus fluid composition (269). Unfortunately, the transplant is unable to achieve the same level of body volume control achieved by two native kidneys due to glucocorticoid therapy interfering with sodium handling, and calcineurin inhibitors altering glomerular filtration pressures and potassium handling. The effect of a trend toward euvolaemia on cardiac preload and filling is controversial. Most studies have used echocardiography to assess chamber dimensions:

- Ferreira et al investigated 28 patients with no evidence of pre-transplant LVSD on echocardiography. They showed that there was a significant reduction in LV end diastolic diameter (LVEDD) 12 months after transplantation (267).
- Dudziak et al performed a similar study in 23 transplant recipients and showed no significant reduction in LVEDD after 3 months from successful renal transplantation (260). Similarly, Oppert et al showed no significant difference in LV chamber size one year after simultaneous pancreas kidney transplantation (270).

The inconsistencies of previous published work highlight the weakness of echocardiography studies in ESRD and transplant recipients. On the other hand, the strength of the present study lies with the use of CMR which allows precise visualisation of epicardial borders and volume independent measurement of the LV chamber and wall.

Thus, based on these data, LV chamber size at end diastole and systole and LV ejection fraction are not affected by renal transplantation. This presumably reflects action of the homeostatic mechanisms that control cardiac preload, such as venous tone, which increase in response to reduced intravascular volume. In addition, increases in LV ejection fraction and reductions in LV mass are most likely an artefact of reduced extracellular and hence intraventricular fluid.

8.4.3 Limitations

Although the current study is limited by small sample size and variability in timing of scans it is the first study to serially evaluate the LVs of patients who have undergone renal transplantation using CMR. Greater precision and reproducibility

of CMR permits smaller, adequately powered studies to be meaningful compared to echocardiography (137). Furthermore, interdialytic changes of haemodialysis patients were reduced by standardising the timing of CMR (24 hours after end of last haemodialysis session) for both scans.

8.5 CONCLUSIONS

Cardiovascular disease remains a major cause of morbidity and mortality after renal transplantation, and this study supports a possible role for LVH. These findings cast doubt on the reversibility of left ventricular hypertrophy in this population and it is likely that prevention, for example by tight blood pressure and bone mineral control, in the earliest phases of progressive renal disease with the aim of preventing development of left ventricular hypertrophy will be a more successful strategy. Moreover, it seems likely that the previous positive results are artefactual due to normalisation of intravascular volume following successful transplantation.

Chapter 9

General discussion and conclusions

9.1 Utilisation of cardiovascular MRI to assess uraemic cardiomyopathy

The principal aims of these studies were to elucidate features of uraemic cardiomyopathy using CMR which account for increased risk of CV (usually sudden cardiac) death in ESRD patients. In particular, these studies addressed:

- The prognostic effect of left atrial and ventricular abnormalities detected by CMR.
- The pathophysiological features of uraemic cardiomyopathy using novel, non-invasive techniques which have been evaluated in other patient populations.

As stated in Chapter 1, greater accuracy and precision of CMR compared to echocardiography for measuring LV mass and chamber dimensions allows smaller sample size to be studied with no loss of statistical power.

9.2 Summary of findings

The strengths of these studies lie with the use of CMR to accurately assess LV abnormalities in ESRD patients. Furthermore these are the largest observational studies using CMR to identify prognostic features of uraemic cardiomyopathy and present important, novel results. Chapters 6 and 7 present data that are novel and provide valuable insight regarding the electrophysiological and metabolic changes associated with uraemic cardiomyopathy.

9.2.1 Determinants and prognostic features of uraemic cardiomyopathy

Figure 9.1 summarises findings from Chapters 3 to 5. The cardiovascular changes of advancing renal disease predispose to development of uraemic cardiomyopathy, namely intravascular volume expansion, hypertension and reduced vascular

compliance. As with other disease states (e.g. advancing heart failure) initial compensatory mechanisms, such as additional sarcomere proliferation, ultimately result in further deterioration of LV architecture. One notable finding from Chapter 3 was a close relationship between different LV abnormalities, which was postulated to represent differing stages of development of uraemic cardiomyopathy. The prognostic effects of LV abnormalities on CV survival were also demonstrated in a large prospective CMR study of ESRD patients (Chapter 4) and results are also summarised in Figure 9.1. Elevated end systolic LAV has been assessed in studies of ESRD patients (207) using echocardiography. However, given the paucity of studies demonstrating convincing reversal of LVH in ESRD patients (which is very common and usually severe) using interventions trialled in the general population, other potentially modifiable cardiac factors independent of LV mass were evaluated (Chapter 5). Elevated LAV also adversely reduced survival of ESRD patients.

9.2.2 Novel pathophysiological features of uraemic cardiomyopathy

Figure 9.2 shows some of the electrophysiological and metabolic abnormalities associated with uraemic cardiomyopathy which were presented in the later chapters of this thesis. In the first study of ESRD patients, the effects of LV structural changes detected by CMR were investigated using MTWA to determine abnormal myocyte repolarisation. MTWA has not previously been used to assess ESRD patients and, as discussed in Chapter 6, may provide additional information to identify subjects at risk of SCD. As well as being independently associated with features of uraemic cardiomyopathy, MTWA was also associated with a clinical history of macrovascular atheromatous disease suggesting that even in the absence of LV abnormalities, patients with occlusive vascular disease develop abnormal

ventricular repolarisation. These early changes are most likely due to microvascular changes and myocardial fibrosis, which may not be evident on CMR examination but are nonetheless common in ESRD patients (49;257). In Chapter 8, novel data were presented demonstrating altered cardiac energetics and HEP metabolism in patients with features of uraemic cardiomyopathy compared to patients with hypertensive LVH. Furthermore, reduced HEP metabolism was independently associated with LVSD of uraemic cardiomyopathy. A smaller study (149) has demonstrated a difference between ^{31}P MRS results of diabetic patients and renal transplantation recipients, but this study uniquely demonstrates a significant association with LVSD and LV dilatation in ESRD subjects.

9.2.3 Effect of successful renal transplantation on left ventricular mass

In Chapter 9, data from a small observational study showed that successful renal transplantation was not associated with a significant regression of LVMI compared to patients who remained on the renal transplant waiting list. These data highlight two issues:

- Previous studies that demonstrated significant reduction in LV mass using echocardiography, were most likely showing artefactual changes by measuring improvement in intravascular and hence LV chamber volume as opposed to reduction in myocardial wall thickness (260;261).
- It is likely that factors, such as hypertension and vascular stiffness remain after renal transplantation and may perpetuate increases in LVMI.

Figure 9.1 Determinants and prognostic features of uraemic cardiomyopathy

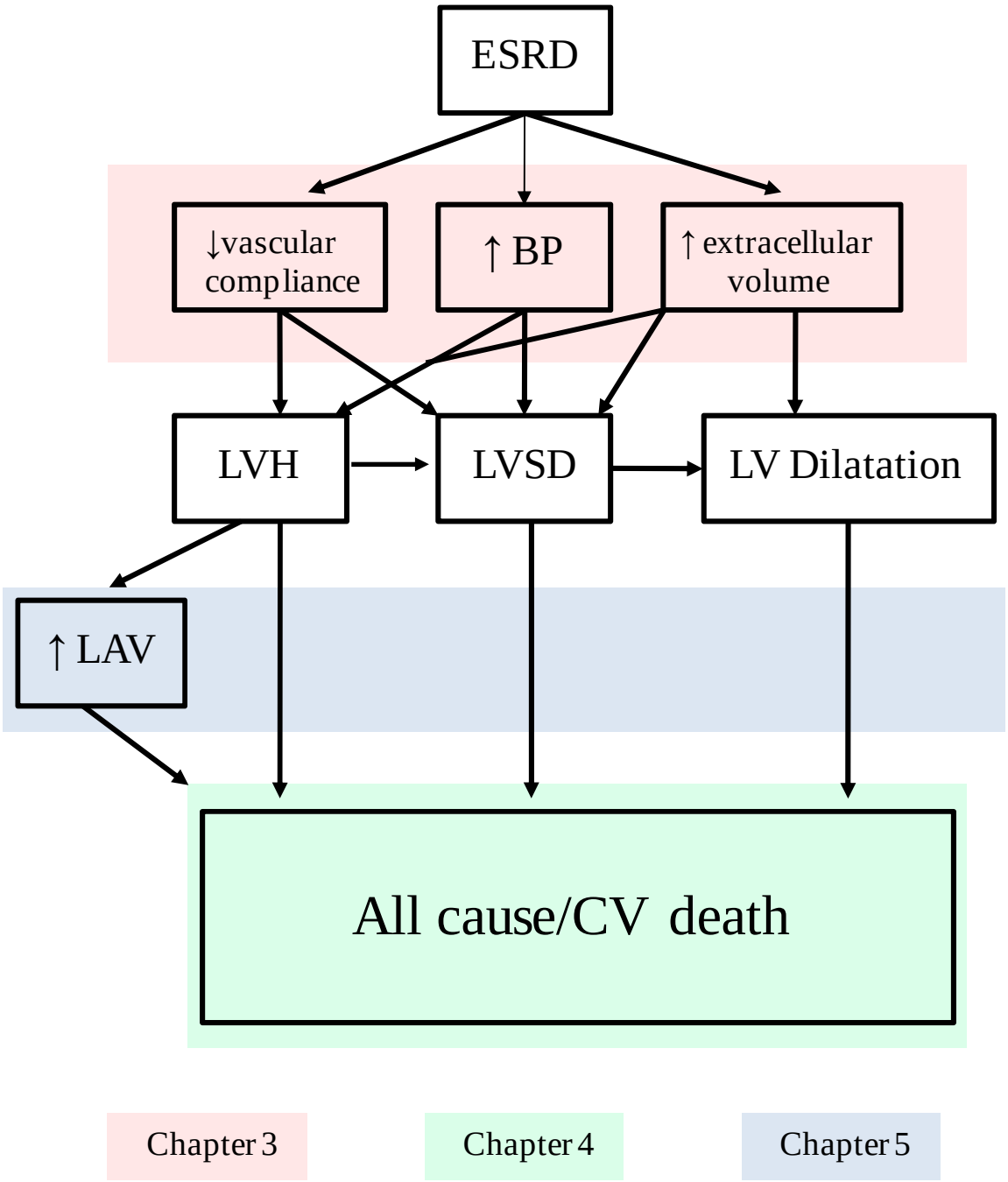
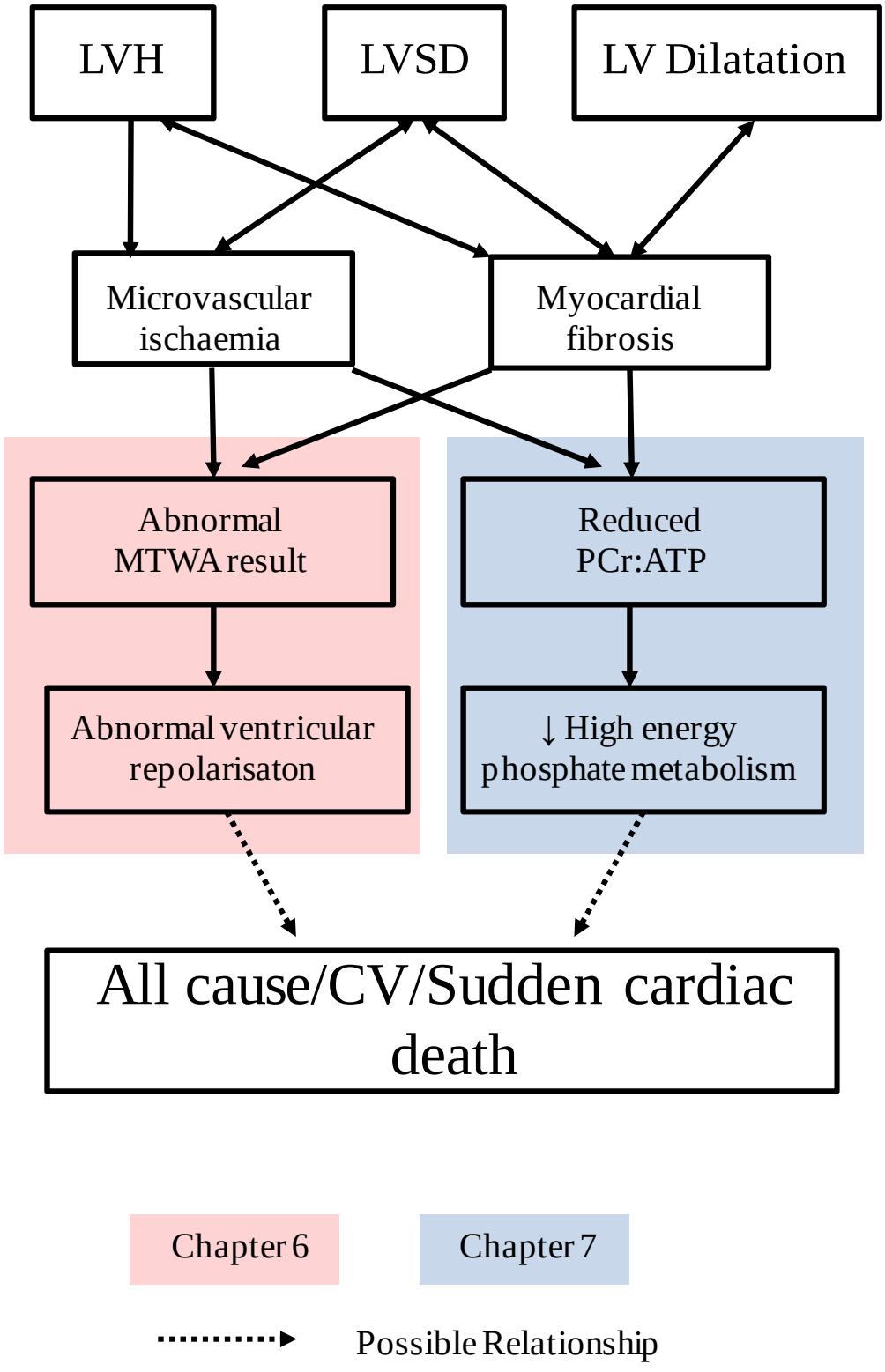


Figure 9.2 Pathophysiological features of uraemic cardiomyopathy



9.3 Limitations of current studies

There are limitations in these studies. In the initial study design, 24 hour ambulatory ECG monitoring was planned to assess sinus rhythm changes and provide more prognostic data for this patient cohort (115). Unfortunately, this was not completed as many patients did not wish to wear ambulatory monitors overnight. However with these data, presence of significant "resting" arrhythmias may have been detected and the additional effect on MTWA result and/or overall risk of CV mortality may have been evaluated. Twenty four hour ECG monitoring is a cheaper and more readily available method of detecting cardiac electrophysiology abnormalities compared to MTWA, however the sensitivity and specificity for identifying ESRD patients at risk of SCD remains to be convincingly demonstrated. In addition, measurement of other cardiac electrophysiological parameters was proposed for study, namely QT dispersion and heart rate variability. However, detection hardware and software were not available by the time of recruitment.

As stated in Chapter 2, patients recruited into these studies were those being assessed for renal transplantation. This cohort has previously been criticised as some investigators believe that this may not provide true cross sectional sampling of patients with ESRD. Historically, patients considered (by a transplant surgeon or nephrologist) likely to survive the peri-operative period were referred for pre-transplant CV assessment. However, since these patients were considered fit enough to be considered for transplantation, it is likely that these results underestimate cardiac abnormalities of ESRD patients and would be relevant to other individuals with more significant co-morbidities.

Although our main aims and objectives were achieved, outcome data based on MTWA and HEP metabolism were not available. Nonetheless, the MTWA study finished recruiting 12 months ago and there was a trend toward reduced survival in the abnormal MTWA group (Chapter 6).

9.4 MTWA and HEP metabolism as predictors of sudden cardiac death

In this thesis, data are presented demonstrating significant abnormalities of cardiomyocyte action potential (AP) propagation and recovery in ESRD patients using MTWA. As stated in Chapter 1, any changes of cell function resulting in abnormal intracellular cation cycling and subsequent non uniform membrane de- and repolarisation may increase risk of re-entrant tachyarrhythmias. Abnormal MTWA results in ESRD patients were associated with features of uraemic cardiomyopathy on CMR examination. T wave alternans develops at higher heart rates due to discordant repolarisation alternans between adjacent cardiomyocytes on an every-other- beat basis. This most likely develops in uraemic hearts due to pathological changes described including abnormal intracellular calcium handling, microvascular ischaemia, interstitial fibrosis and inadequate metabolic substrate availability.

Abnormal MTWA was also independently predicted by clinical history of peripheral and cerebrovascular atheromatous disease, implying that other forms of macrovascular disease are associated with abnormal ventricular repolarisation. Metabolic abnormalities can be measured non- invasively using ^{31}P MRS and in the future it will be interesting to evaluate the additional prognostic effect of these MRS results with MTWA on development of SCD.

9.5 Future studies

A striking feature of these studies was the high proportion of ESRD patients with established LV abnormalities, even in the pre-dialysis period of renal disease, implying that these changes develop in the earlier stages of CKD. Regression of uraemic cardiomyopathy, especially LVH, has been difficult to achieve thus prevention needs to be assessed. With the use of eGFR to identify patients with earlier stages of CKD, future studies may allow early cardiac assessment to detect onset of cardiomyopathy and potentially modifiable aetiological factors

Prior to the discovery of anassociation with nephrogenic systemic fibrosis (NSF) in patients with advanced renal disease, gadolinium based contrast CMR provided useful diagnostic and prognostic information in ESRD patients. These agents are no longer considered to be safe in patients with advanced renal dysfunction. However macrocyclic chelating agents (such as gadoteridol) are associated with a lower risk of NSF and the only group of Food and Drink Administration approved agents for clinical investigation in patients with advanced renal disease (271). Nonetheless, the use of these agents has to be weighed against the benefit of the diagnostic procedure and availability of other imaging modalities. These agents are obviously not appropriate in a research setting.

Blood oxygen level- dependent (BOLD) contrast CMR is based on the differing magnetic properties of oxyhaemoglobin and deoxyhaemoglobin which can be detected by T1 and T2* weighted scans. As a result, areas where oxyhaemoglobin concentrations are high (coronary blood perfusion is greater than myocardial demand) can be visualised. Conversely, areas of myocardial ischaemia can be

detected without the use of gadolinium based contrast agents. Blood oxygen level-dependent CMR has been used to detect myocardial ischaemia in animal models of coronary artery occlusion and in patients with inducible myocardial ischaemia due to large and small vessel coronary artery disease (272-274). The prognostic implications for BOLD contrast CMR remains to be elucidated, however given the high prevalence of small and large vessel ischaemic heart disease in ESRD patients, this may be a CMR technique that could be pursued in the future. Alternative non gadolinium contrast agents include superparamagnetic iron oxide particles (SIOP) which has also been investigated for their potential role of quantifying not only myocardial stress perfusion but areas of fibrosis and previous myocardial infarction (similar to gadolinium contrast scans) (275). To this end, these agents may also provide a safe means of performing contrast enhanced scans in patients with ESRD.

Data from Chapter 7 support earlier studies performed in animal models of uraemic cardiomyopathy demonstrating abnormal metabolic function in apparently normally contracting myocardium. Given the relative small size of this study, these data could be used to power larger prognostic studies in patients with ESRD once outcome data are available. Furthermore, other nuclei have been investigated using MRS. ^{1}Hydrogen allows quantification of myocardial fat content, lactate, carnitine, deoxyhaemoglobin and total creatine levels which are reduced in patients with heart failure (276). However these studies are limited due to the high level of ^{1}H within cardiomyocytes (mostly in the form of water), which may provide even greater technical difficulties in patients with ESRD where total body water is increased.

Finally, further investigation of CV changes that occur after renal transplantation may provide insights to potential modifiable factors in patients with ESRD. In this thesis, renal transplantation was not associated with significant regression of LV mass after a mean period of 1.8 years. It is possible that a longer follow up would be necessary to demonstrate a significant reduction, however post transplant hypertension is one of the major side effects of long term immunosuppression and most likely perpetuates rising LV mass. Alternative studies could include ^{31}P MRS to determine the effect of reduced "uraemic" toxins and better intravascular fluid control after successful renal transplantation. Similarly, measurement of aortic compliance and vascular stiffness using CMR has been performed in ESRD patients (203), and an interesting study would be to assess the effect of renal transplantation on these parameters.

9.6 Reducing cardiovascular disease in ESRD patients

The main aims of the KDIGO guidelines for identifying patients with early CKD was not only to slow progression of renal dysfunction, but to address the concomitant rise in CV disease (2). Unfortunately, this subject has a paucity of well controlled and adequately powered interventional studies demonstrating convincing evidence of benefit for ESRD patients. However, it is postulated that given the association of CV death and uraemic cardiomyopathy presented in Chapter 4, slowing or preventing development of LV architectural changes may be an attractive target for intervention.

9.6.1 Preventing development of uraemic cardiomyopathy

Preventing development of uraemic cardiomyopathy remains an attractive target in early stages of kidney disease. Data presented in Chapter 3 demonstrate that features of CKD (e.g. hypertension, vascular stiffening) are associated with the development of uraemic cardiomyopathy and that LV abnormalities are closely associated once cardiomyopathy is established. Unfortunately, attempts to alter other established CV risk factors in ESRD patients, such as dyslipidaemia, have shown no significant survival benefit (AURORA, 4D). Although not entirely evidence based, aggressive management of other established cardiovascular risk factors in earlier stages of kidney disease, in particular hypertension, may slow or reduce prevalence of uraemic cardiomyopathy and subsequent CV morbidity and mortality. In addition, other novel and renal specific risk factors need to be identified that predispose to CV disease and may be amenable to intervention to prevent development of uraemic cardiomyopathy.

Chronic expansion of extravascular volume is a hallmark of advancing renal disease and has been shown in these and other studies to be a potential aetiological factor for development of LV abnormalities (169;170). In practice, however, control of body fluid volume is predominately dictated by patient symptoms (peripheral and pulmonary oedema) and/or “dry” or “ideal” body weight in more advanced stages of CKD. Tighter control of fluid balance with oral restriction and diuretic therapy at earlier stages of renal dysfunction may reduce development of uraemic cardiomyopathy. Unfortunately, patient compliance remains a major restricting factor particularly when interventions have unpleasant side effects (e.g. xerostomia and excessive micturition). More objective means of measuring body fluid status,

such as bioimpedance spectroscopy, may provide more convincing evidence to pursue these studies further (194).

Furthermore, bone mineral disorder is associated with development of LVH in ESRD patients implicating arterial stiffness as an aetiological factor for uraemic cardiomyopathy. Although not a conventional risk factor for CV disease, intervention at an early stage of bone mineral disorder, perhaps before development of significant secondary hyperparathyroidism would be appropriate (current Renal Association guidelines state that vitamin D analogue therapy should start when parathyroid hormone therapy is 2-4 times upper limit of normal range) (42). Both KDIGO and Renal Association guidelines highlight the need for prospectively controlled studies addressing the benefit for treatment of bone mineral disorders in earlier stages of renal dysfunction (277).

9.6.2 Reversing uraemic cardiomyopathy

Preventing development of uraemic cardiomyopathy has been the most attractive option in patients with CKD because reversal, once established, has been very difficult to achieve. The absence of prospective studies has made development of evidence based guidelines for reversal of uraemic cardiomyopathy in patients with established ESRD difficult. There are a number of factors that have been presented in this thesis and other studies that merit further evaluation in such studies.

Tight control of intravascular and extracellular volume is an important factor. In Chapter 3, extracellular volume was a significant determinant of development of LVH, LVSD and LV dilatation. As with CKD patients, this can be achieved with

rigorous adherence to fluid and salt restriction to reduce interdialytic weight gains for haemodialysis patients and use of diuretic therapy in patients with residual renal function. Excessive intradialtytic ultrafiltration may provide some benefit, however this should be performed with caution given increased risk of myocardial stunning and intradialytic hypotension (70). A small (n=25) prospective study in Scottish haemodialysis patients has been performed to assess the effect of intradialytic bioimpedance monitoring over 6 months on a number of CV parameters including LV mass measured by CMR. These data will be presented within the next 6 months.

The use of antihypertensive pharmacological agents needs to be fully assessed. Blood pressure (including pulse pressure) control may be partially achieved by controlling intravascular volume adequately. Nonetheless, from small prospective trials using beta blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers mentioned in Chapter 1, some benefit has been demonstrated in patients with ESRD (120;125). Whether these agents improve outcome independently of blood pressure control in ESRD patients remains to be assessed. Despite these findings, cardioactive medications remain grossly underused even in ESRD patients who have developed significant CV morbidity (36) indicating that a change in clinical practice needs to be implemented.

More frequent and greater quality of dialysis may reverse uraemic cardiomyopathy in haemodialysis patients. Reduction of LV mass measured by CMR has been demonstrated in small prospective and observational studies in haemodialysis patients treated with frequent and/or nocturnal regimens compared to conventional thrice weekly haemodialysis (20;278). The findings of the Frequent Haemodialysis

Network randomised controlled trial investigating frequent haemodialysis (daily in-centre and nocturnal home haemodialysis) with conventional thrice weekly regimen are due within the next 6 months and has CMR measured LVMI as a composite end point. Furthermore, more efficient removal of solutes using high flux dialysis membranes has been associated with longer survival in hypoalbuminaemic haemodialysis patients compared to those treated with conventional low flux ones (279). Whether this type of dialysis improves LV myocardial changes remains to be evaluated.

In Chapter 8, absence of reduction of LV mass after renal transplantation was attributed to post transplant hypertension (possibly related to calcineurin inhibitor use), bone mineral disease and intravascular expansion. Further study of transplant recipients with older grafts, tighter control of blood pressure and fluid status, or usage of lower dose/alternative immunosuppressive agents may also demonstrate significant changes in myocardial architecture.

The effect of treatment of ESRD related bone mineral disorders on reversal of uraemic cardiomyopathy has not been established. Use of non calcium based phosphate binders is associated with reduced coronary calcification and improved survival in haemodialysis patients (280). Furthermore, in primary hyperparathyroidism patients with no renal disease parathyroidectomy is associated with reduction of LV mass (281). Whether treatment of hyperparathyroidism by surgery or newer calcimimetic agents affect uraemic cardiomyopathy would be an interesting study to pursue.

Finally, the benefit of ICD insertion in ESRD patients needs to be established. In a recent meta- analysis of dialysis patients with ICDs (n=89), there was still significantly elevated CV mortality in ESRD patients (282) compared to ICD recipients with milder renal diseases. A prospective pilot study assessing ICD insertion in dialysis patients (ICD2) has recruited 200 patients in the Netherlands and plans to report outcome data in 2012 (283).

As with studies in patients with heart failure, careful selection of patients is required to identify those who would benefit most from pharmacological or ICD intervention. The results of studies presented in this thesis aim to provide information for selecting ESRD patients at higher risk of CV or sudden cardiac death (Figure 9.3). With these results in mind, further prospective studies will be able to carefully select groups of ESRD patients with differing left ventricular, left atrial, electrophysiological and biochemical properties to demonstrate survival benefit with specific interventional agents. In this way, future therapies for ESRD patients can be tailored to improve cardiovascular survival.

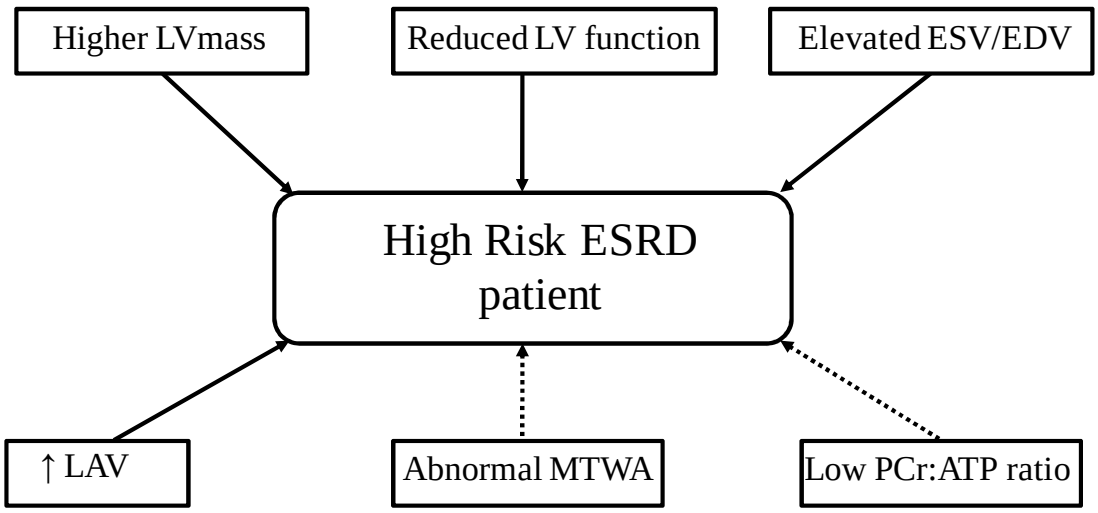


Figure 9.3 Possible features of ESRD patients who are at an increased risk of cardiovascular or sudden cardiac death

9.7 CONCLUSIONS

- Premature, usually sudden, cardiovascular death is the commonest cause of death in patients with end stage renal disease.
- Elevated risk of cardiovascular death is due to higher prevalence of traditional, novel and uraemic specific cardiovascular risk factors.
- Abnormalities of left ventricular structure (LV hypertrophy, dysfunction and dilatation), collectively termed uraemic cardiomyopathy have been implicated with higher cardiovascular mortality.
- Cardiovascular magnetic resonance imaging is the most accurate and volume independent method of assessing myocardial structure in ESRD patients. Furthermore, ^{31}P magnetic spectroscopy is a method which non- invasively assesses cardiac metabolic activity.
- Hypertension, presence of bone mineral disorders and expanded extracellular volume are common features of advanced CKD and are major determinants of presence of LVH, LVSD and LV dilatation on CMR.
- LVSD and LV dilation detected by CMR are associated with reduced all cause and CV survival in ESRD patients. LVH is significantly associated with reduced cardiovascular survival. End stage renal disease patients with two or more cardiac abnormalities on CMR have a significantly poorer prognosis.
- High LAV and presence of LVSD are associated with poorer all cause survival and independent predictors of mortality in ESRD patients with LVH.
- Microvolt T Wave Alternans is a novel, non invasive electrophysiological technique of measuring variability in ventricular repolarisation and is associated with development of life threatening tachyarrhythmias. Abnormal MTWA result is more common in ESRD patients compared to hypertensive LVH patients and is

significantly associated with uraemic cardiomyopathy and a history of macrovascular atheromatous disease in ESRD patients.

- End stage renal disease patients have lower HEP metabolism compared to hypertensive LVH patients despite similar LV mass. Lower PCr: βATP ratio is associated with features of uraemic cardiomyopathy
- Successful renal transplantation is not associated with significant regression of LVH when measured by CMR.
- Future studies may use these pathophysiological and prognostic features of uraemic cardiomyopathy to identify patients suitable for interventions which improve cardiovascular survival in ESRD patients.

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11.0 APPENDIX

Publications containing work undertaken for this thesis:

Patel RK, Mark PB, Johnston N, McGeoch R, Lindsay M, Kingsmore DB, Dargie HJ, Jardine AG. Prognostic value of cardiovascular screening in potential renal transplant recipients: a single-center prospective observational study. Am J Transplant. 2008 Aug;8 (8):1673-83

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Patel RK, Mark PB, Cobbe SM, Jardine AG. Microvolt T wave alternans in end stage renal disease patients- association with uremic cardiomyopathy. Accepted for publication. Clin J Am Soc Nephrol September 2010.

Publications related to the work in this thesis:

Mark PB, Patel RK, Jardine AG. Are we overestimating left ventricular abnormalities in end stage renal disease. Nephrol Dial Transplant. 2007 Jul;22(7):1815-9.

McQuarrie EP, Patel RK, Mark PB, Delles C, Connell J, Dargie HJ, Steedman T, Jardine AG. Association between proteinuria and left ventricular mass index: a cardiac MRI study in patients with chronic kidney disease. Nephrol Dial Transplant. 2010 Jul 12.