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An Analysis of Myocardial Deformation with Speckle Tracking Echocardiography in Black Patients on Haemodialysis

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Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of the Master of Science in Medicine.

Johannesburg

2013

Declaration:

I, Anthony Yip, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature ……

……..day of……2013

Dedication

I would like to dedicate this work to my mother, Lida, and father, Lawrence, for their unwavering support and guidance throughout my life, and to my sister, Veda, for being there during the challenging times.

I am grateful to Dr John A. Elefteriades for his considerable gifts as a surgeon and compassion as a physician that made it possible for me to complete this work.

Publications and presentations arising from this study:

Abstracts presented

Myocardial twist characteristics in an African chronic kidney disease population on haemodialysis before and after dialysis as measured by speckle tracking echocardiography

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Publications:

The following article arising from work done in this dissertation has been submitted to journals for review:

Left Ventricular Twist before and after Haemodialysis: An analysis using Speckle Tracking Echocardiography.

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ABSTRACT

Cardiac disease is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD). Accurate evaluation of cardiac function is therefore important but difficult with commonly used imaging modalities such as echocardiography being subject to variable load changes in haemodialysis.

This dissertation examines the close association in pathology between the two organ systems. Specifically, it explores the role of CKD and the uraemic state in the pathogenesis of cardiac disease. The cardiac manifestations in renal disease ranges from left ventricular hypertrophy (LVH) with diastolic dysfunction to ischaemic heart disease and sudden cardiac death (SCD).

The current imaging modalities available for assessing the heart are explored. We evaluate the universally used transthoracic echocardiography, the insights it has provided in our understanding of cardiac pathology in the renal patient, and its limitations. Other currently used imaging modalities such as magnetic resonance imaging (MRI), single positron emission computed tomography (SPECT), and multigated acquisition imaging (MUGA) are discussed. The main limitation of these imaging modalities in assessing cardiac pathology in CKD are the variable load and metabolic changes that occur during dialysis. These variable changes make the accurate measurement of left ventricular systolic function difficult.

Myocardial deformation is the change of shape and motion of the myocardium. Strain refers to a change in length in the myocardium relative to its initial length in response to an applied force. It is a dimensionless measurement used to measure myocardial deformation. Strain imaging using tissue Doppler imaging (TDI) and more recently speckle tracking echocardiography (STE) have emerged as promising techniques in evaluating myocardial function. A few studies have suggested that strain imaging may hold some promise in the early detection of cardiac disease in the CKD patients.

This pilot study evaluated the use of myocardial deformation analysis using speckle tracking echocardiography (STE) as a relatively load independent measure of cardiac function in CKD patients on dialysis. It showed that there were no significant changes in the chief forms of myocardial deformation: longitudinal strain (14.2 ± 3.0 % vs. -13.4 ± 3.0 %, p = 0.07), circumferential strain (-17.4 ± 4.8 vs. -16.9 ± 5.1, p = 0.61), radial strain (10.8 ± 6.4 vs. 19.9 ± 17.6, p = 0.09) and left ventricular twist (9.6^{o} ± 1.9 vs. 8.2^{o} ± 3.1, p = 0.01) before and after dialysis, despite a change in ejection fraction (58.8 ± 13.7 vs. 61.2 ± 13.6, p= 0.02). In addition, components of strain: apical rotation (6.31^{o} ± 1.6 vs. 4.83^{o} ± 2.3, p = 0.01) and global radial strain (27.88 ± 1.35 vs. 10.8 ± 6.4; p<0.01) were diminished in CKD compared to values in matched normal subjects though no difference in EF (61.7 ± 6.2 vs. 58.8 ± 13.7, p = 0.68) was seen.

The conclusions of this study are that: 1) myocardial deformation may represent a novel measure of cardiac function in the CKD patient on dialysis which is less sensitive to load changes than Ejection Fraction measurements; and 2) apical rotation may identify a more sensitive marker of cardiac pathology in the CKD patient with preserved ejection fraction.

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ABBREVIATIONS

ADQI	Acute Dialysis Quality Initiative
AP4C	apical four chamber view
BMI	body mass index
BSA	body surface area
CAD	coronary artery disease
CKD	chronic kidney disease
EF	ejection fraction
ε (epsilon)	mathematical symbol for strain
FS	fractional shortening
GCS	global circumferential strain
GLS	global longitudinal strain
GRS	global radial strain
GPCS	global peak circumferential strain
GPLS	global peak longitudinal strain
GPRS	global peak radial strain
IVSD	interventricular septal diameter
KDIGO	Kidney Disease: Improving Global Outcomes
LA	left atrium
LAV	left atrial volume
LAVI	left atrial volume index
LAX	long axis view
LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume

LVESD	left ventricular end-systolic diameter
LVESV	left ventricular end-systolic volume
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
MAP	mean arterial pressure
MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
MUGA	multigated acquisition
PP	pulse pressure
PP/SV	pulse pressure/ stroke volume
PTH	parathyroid hormone
RWT	relative wall thickness
SAX	short axis view
SCD	sudden cardiac death
SPECT	single positron emission computed tomography
STE	speckle tracking echocardiography
SV	stroke volume
TDI	tissue Doppler imaging

1. INTRODUCTION

Chronic kidney disease (CKD) is associated with considerable cardiovascular morbidity and mortality with cardiac pathology accounting for approximately half of all deaths in this group (1). Sudden cardiac death accounts for 52% of these deaths(2).The reason for this association may be the shared risk factors such as hypertension, diabetes and dyslipidaemia which are implicated in atherosclerotic cardiac and renal diseases. The observations that the incidence of coronary artery disease (CAD) increases with decreasing glomerular filtration rate, and that over 50% of patients with CKD requiring dialysis will have CAD, might support this supposition(3). However, traditional risk factors do not fully explain the high incidence of cardiovascular events and mortality(4). Renal disease itself has pathophysiological effects on the heart. Clearly, the two organ systems are closely linked.

The association between the cardiac and renal systems in health and disease has led to the acknowledgment of the cardio-renal syndromes as real entities. A consensus document, drawing on the expertise of nephrologists and cardiologists under the auspices of the Acute Dialysis Quality initiative (ADQI), defined the 'cardio-renal syndromes as disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ system leads to acute or chronic dysfunction in the other' (5). Five categories of cardio-renal syndromes exist: 1) acute cardio-renal syndrome; 2) chronic cardio-renal syndrome; 3) acute reno-cardiac syndrome; 4) chronic reno-cardiac syndrome; and 5) systemic illnesses that lead to combined cardiac and renal dysfunction. These syndromes can

roughly be summarised as cardiac disorders that lead to secondary renal dysfunction (cardio-renal) and renal condition that lead to secondary cardiac dysfunction (reno-cardiac). **Fig.1**

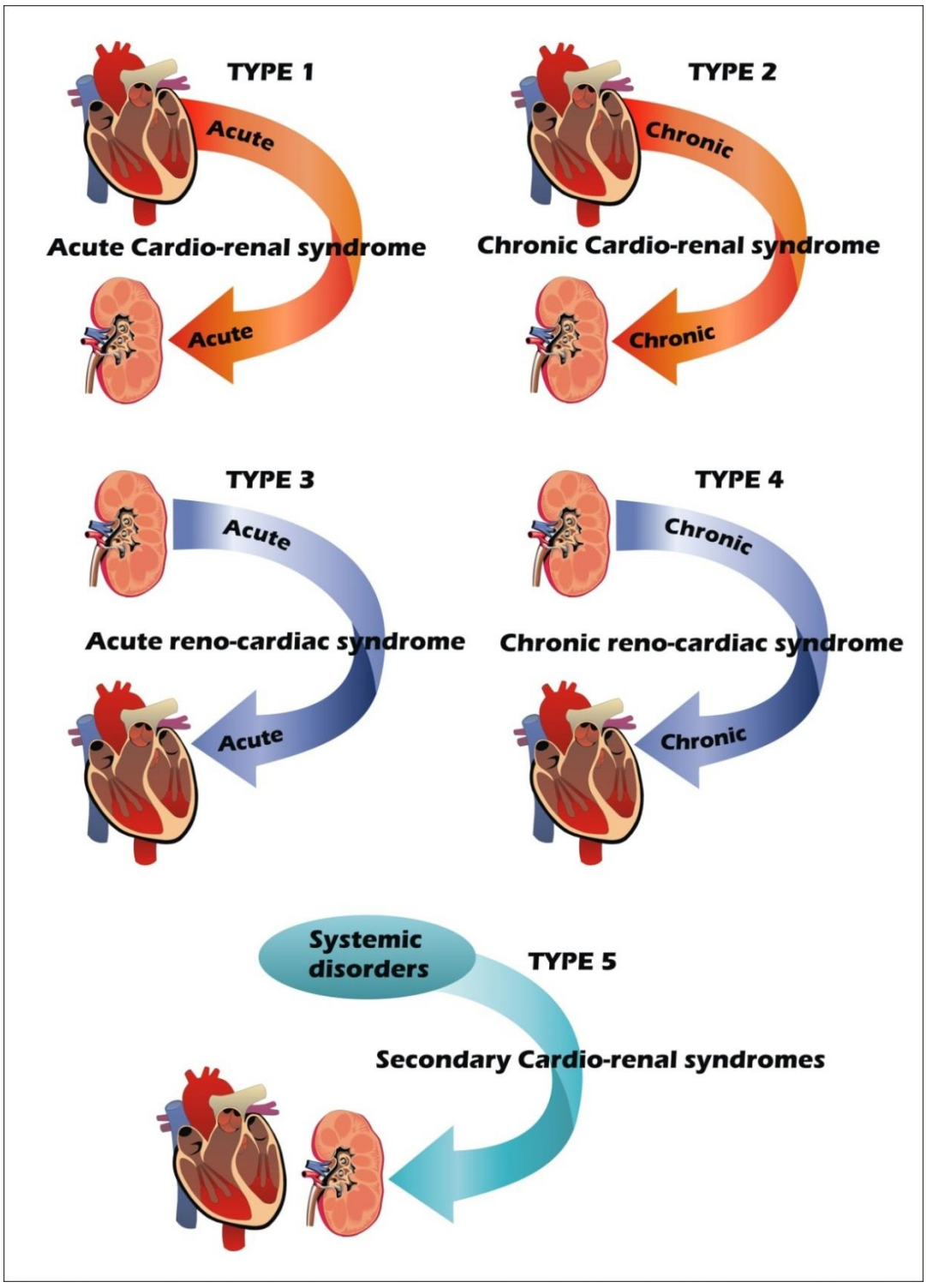


Figure 1 From the ADQI consensus document on cardiorenal syndromes. Ronco, C. et. al. Eur Heart J. 2010; 31(6):703-11. Epub 2009/12/29.

This dissertation explores the forms of cardiac pathologies which occur in CKD (type 4 reno-cardiac syndrome). It briefly discusses the pathogenesis of these manifestations; and the current imaging modalities available to assess the heart in patients with CKD.

Because of the importance of cardiac pathology in the morbidity and mortality of CKD patients, imaging modalities that are able to offer an accurate assessment of the structure and function of the heart are essential. A variety of modalities including echocardiography, nuclear imaging and magnetic resonance imaging (MRI) have been utilised for this purpose(6). However, evaluating the heart in CKD remains uniquely challenging: the variable load and metabolic changes in CKD make the precise measurement of myocardial function difficult.

Echocardiography remains the most commonly used method to assess the heart of the CKD patient. Despite its limitations, it is relatively easy to use and has made unique contributions to our understanding of the range of cardiac changes in renal disease and their prognostic importance (6-10). For this reason, new techniques that are able to utilise echocardiography but are able to address the limitations of conventional echocardiography and improve our understanding of cardiac function in CKD would be worth exploring.

Speckle tracking echocardiography is a novel technique in which program algorithms divide ultrasonographically acquired images into small, precise packages of ‘speckles’ which are stable groups of between 20 to 40 pixels that are accurately tagged and followed throughout the cardiac cycle. Speckle tracking echocardiography is used to

measure strain or myocardial deformation which explores the change of length of myocardial fibres in four forms: 1) longitudinal, 2) circumferential, 3) radial, and 4) twisting motions; and provides a unique way to describe and evaluate myocardial function.

The pilot study, conducted as part of this dissertation, explored the utility of myocardial deformation analysis using the unique technique of speckle tracking echocardiography in CKD before and after dialysis. The study evaluated the effects of the variable load conditions of haemodialysis in the CKD patient on myocardial deformation using STE measured strain analysis.

2. LITERATURE REVIEW:

2.1. Epidemiology of cardiovascular pathology in chronic kidney disease

Cardiovascular mortality is ten to twenty times more common in patients with CKD compared to the normal population(11). The majority of patients with CKD entering dialysis will have some form of cardiac abnormalities which include: 1) coronary artery disease (CAD); 2) left ventricular hypertrophy with diastolic dysfunction; 3) congestive heart failure; 4) pericardial diseases including effusions; and 5) sudden cardiac death.(2, 12)

2.1.1. Ischaemic heart disease in CKD patients

Coronary artery disease is prevalent in over half of patients with advanced CKD as seen with small post mortem, angiographic and intravascular ultrasound studies showing diffuse multi-vessel, calcified CAD in this group(13-15). These studies further showed that atherosclerotic CAD became progressively more severe with worsening glomerular filtration rate (GFR). There is no doubt that traditional risk factors such as hypertension, dyslipidaemia and diabetes, are responsible for both cardiovascular and renal disease. However, morbidity and mortality remains higher than expected even when these risk factors are corrected for (16, 17).

The contribution by traditional risk factors is attenuated with advancing disease and paradoxically, the phenomenon of 'reverse epidemiology', suggests that obesity, dyslipidaemia and hypertension may be protective as renal failure progresses(18).

However, it probably reflects the deleterious effects of overly aggressive management of risk factors such as hypertension in patients suffering from a relatively malnourished state. Thus, it appears that the pathophysiological changes associated with CKD itself contribute directly to CAD.

It has been postulated that the following mechanisms lead to the acceleration of CAD in the CKD patient: 1) oxidative stress and inflammation(19); 2) mineralocorticoid excess(20); 3) abnormalities in mineral and bone metabolism(21, 22); and 4) a proliferation of growth and fibroblast factors(23).

Obstructive CAD is not the only cause of ischaemia in CKD patients; dialysis itself may cause repetitive myocardial stunning and ischaemia(24). This phenomenon was demonstrated in a study by McIntyre et al. where myocardial perfusion imaging (MPI) was performed on CKD patients without documented CAD before and after dialysis. Regional ischaemia was demonstrated by MPI leading to the conclusion that repetitive ischaemia and stunning may contribute to myocardial remodelling and uraemic cardiomyopathy.

2.1.2. Left ventricular hypertrophy, the uraemic cardiomyopathy and left ventricular failure

Though ischaemia plays a pivotal role in the genesis of the structural and functional changes of the heart in CKD patients termed the ‘uraemic cardiomyopathy’, there are other haemodynamic and cellular mechanisms at play. There are three chief mechanisms

in CKD that lead to progressive changes in the myocardium from left ventricular hypertrophy to the syndrome of congestive heart failure: 1) pressure overload; 2) volume overload; and 3) non-haemodynamic factors that include proliferation of inflammatory, hormonal and growth factors that alter myocardial structure at a cellular level(3, 25).

Chronic pressure overload is largely a result of hypertension and decreased arterial compliance that is seen in CKD patients. Chronic volume load is a result of the increased salt and fluid status in CKD, anaemia (from reduced erythropoietin production) and arteriovenous fistulae which result in flow overload from a chronic high output state. Both these chronic preload and afterload states lead to increased wall stress on the left ventricle. In turn, this leads to left ventricular hypertrophy, diastolic dysfunction, and systolic dysfunction over time.

The histological hallmark of uraemic cardiomyopathy is myocardial fibrosis (26, 27), which is more severe than that seen in non-uraemic hypertensive hearts with similar degrees of hypertrophy(28). The stimuli for this interstitial fibrosis in the uraemic myocardium include: increased renin-angiotensin; secondary hyperparathyroidism which is thought to have direct toxic effects on the heart(29); reduce erythropoietin; chronic inflammation; and repeated ischaemic stunning(25). In addition to fibrosis, there is a reduction in the capillary density in the uraemic myocardium which is inadequate for the degree of hypertrophy seen(30). This myocyte-capillary mismatch is not seen to the same extent in hypertensive hypertrophy alone and appears unique to the uraemic patient(25). These cellular changes make the uraemic heart prone to further ischaemic injury (shown in rat models) leading to infarct sizes larger than might have been anticipated with the degree

of coronary artery occlusion (31). The cumulative injury to the heart, regardless of the mechanism, with on-going haemodynamic stress leads to apoptosis and programmed cell death which cause further remodelling and progressive heart failure syndromes.

Despite these changes, systolic dysfunction is seen in only about 15% of patients with CKD entering a dialysis programme(8), and heart failure (diastolic and systolic) is only the second most common cardiac cause of death in this patient population.

2.1.3. Sudden Cardiac Death in CKD

Sudden cardiac death (SCD) is the single most important cause of death in patients with CKD accounting for 26% of deaths or a 7% per year mortality risk (2, 32, 33). The aetiology of SCD is thought to be obstructive CAD and fatal arrhythmias(2). Though it was previously supposed that CAD accounted for the majority of SCD, dialysis patients who were revascularised using stents or CABG retained about an 8% annual risk of mortality from SCD. This implied that obstructive CAD did not adequately account for the SCD risk. The mechanisms accounting for and providing the substrates for the increase risk of fatal arrhythmias include : 1) left ventricular dysfunction; 2) left ventricular hypertrophy ; 3) myocardial fibrosis from uraemia; 4) previous myocardial infarction; 5) electrolyte imbalances; 6)Increased calcium/phosphate product; 7) dysautonomia; and 8) repetitive micro-vascular ischaemia and stunning(34).

In a study by Wang et al, it was found that the single most important association with SCD in haemodialysis was systolic dysfunction(33) which is in keeping with findings made in non-haemodialysis patients with and without ischaemia as shown in the MADIT II, SCD

Heft and COMPANION trials(35, 36). These studies confirmed that an ejection fraction of 35% or less was associated with increased risk of SCD from arrhythmias.

2.1.4. Disorders of Bone Mineral Metabolism

The Renal osteodystrophy seen in CKD has been implicated in ischaemic heart disease, LV hypertrophy, cardiomyopathy and sudden cardiac death(37). Chronic kidney disease leads to a decrease production of 1, 25 OH vitamin D levels which results in decreased serum calcium, secondary hyperparathyroidism and hyperphosphataemia.

Increased phosphate is a potent stimulator of vascular calcification primarily in the media of vessels, which increases the arterial stiffness of vasculature(38). This dystrophic calcification was thought to be incidental since it did not affect the conduit function of arteries in the way that atherosclerotic plaque is associated with intimal calcification and luminal stenosis. However, increasing evidence suggests that increased vascular calcification has prognostic implication beyond traditional Framingham risk factors(39). It is thought that this medial calcification may impact on the endothelial function of vessels and partially explains how non-critical atherosclerotic plaques in CKD patients could lead to ischaemic events(37). Hence, increased arterial stiffness with its subsequent left ventricular hypertrophy together with endothelial dysfunction results in increased subendocardial ischaemia especially in patients with co-existing atherosclerosis.

In comparison, serum calcium levels do not have a direct predictive effect for cardiovascular mortality; a study by Foley et al. showed that a serum calcium of less than

2.2 mmol/L is associated with in an increased mortality(40); in contrast, a study by Chertow et al. showed the opposite: with a decreased mortality in patients with calcium levels less than 2.0 mmol/L (41). Underlying parathyroid hormone (PTH) status may be a far better reflection of bone mineral metabolism than serum calcium in this regard.

It has been a long-held belief in the nephrology community that an increased calcium phosphate product is associated with increased visceral and vascular calcification. Indeed, evidence suggests that for every $10g^2dl^2$, there is an increased relative risk of 1.06 for death from CAD and 1.07 relative risk of SCD(42). However, the serum phosphate level is likely the greater contributor to this risk. In addition, it is not clear whether a single value is of importance or a sustained period above a threshold calcium x phosphate product level will have greater prognostic value(37).

In a large study looking at 14 829 dialysis patients from the United States Renal Data Systems, quintiles of: 1) albumin corrected calcium; 2) phosphate; 3) calcium phosphate product; and 4) PTH levels showed that increasing levels of each factor correlated directly with an increased risk of cardiovascular events and all-cause mortality.(43)

These results appear to contradict the earlier report by Foley et al. that low serum calcium was associated with increased mortality. The CHOICE (Choices for Healthy Outcomes in Caring for End-stage Renal Disease) study tried to clarify this issue.(44) This study showed that baseline values of serum calcium and PTH were not of prognostic value in itself (which may have been a limitation of Foley's original paper); however, if

analysed in a time dependent manner then increased levels of calcium and PTH were associated with increased all-cause mortality.

Despite these controversies, an awareness of the abnormal values in bone mineral metabolism adds to our understanding of the pathophysiological factors at play in the cardiac manifestations in kidney disease.

2.2. The value of cardiac imaging in chronic kidney disease

With the importance that cardiac pathology has in the morbidity and mortality of patients with CKD, it is clear that accurate assessment of both the structure and function of the heart is important.

There are a number of imaging modalities that are currently used in this regard: 1) echocardiography; 2) magnetic resonance imaging (MRI); 3) multigated image acquisition (MUGA); and 4) single positron electron computerised tomography (SPECT) scanning(6, 7, 10, 45).

2.2.1. Echocardiography

Echocardiography is the most commonly used imaging modality used in assessing both structure and function of the heart in patients with renal disease. It has the advantage of relative ease of use; reproducibility; is non-invasive; is portable; is relatively cost-

effective; and has been validated in a wide variety of cardiac conditions over the last forty years (6, 46).

Much of our knowledge of cardiac changes in CKD has been provided by echocardiographic based studies. In a seminal, prospective study conducted by Foley et al.(8), it was found that 85% of CKD patients will have some form of cardiac changes on echocardiography (8, 47).

The most common changes seen are 1) left ventricular hypertrophy (LVH); 2) diastolic dysfunction; 3) evidence of ischaemic heart disease; 4) valvular abnormalities; 5) pericardial changes; and 6) systolic dysfunction which is only seen in about 15% of patients

2.2.1.1. Left ventricular hypertrophy

Left ventricular hypertrophy(LVH)is highly prevalent in patients with CKD and is present in about 85% of patients with CKD.(8) The incidence of LVH increases with decreasing GFR with the following incidence: 16 to 31% in patients with a GFR > 30ml/min(48); 38 to 45% with a GFR <30ml/min; 60 to 75% at the start of dialysis; and 80 to 90% with patients on established dialysis(49, 50).

Left ventricular hypertrophy has prognostic implications. Two thirds of patients with CKD and LVH will die of diastolic dysfunction or sudden cardiac death.(10)

Patterns of hypertrophy also appear to be important. Concentric hypertrophy has been associated with a median survival of 48 months while eccentric hypertrophy is associated with a median survival of 56 months.(9)

2.2.1.2. Diastolic dysfunction

Fifty to sixty five percent of CKD patients will have some degree of diastolic dysfunction which is associated with increased morbidity and mortality(51). Diastolic dysfunction is measured in echocardiography either by transmitral pulse wave Doppler or tissue Doppler imaging over the medial or lateral mitral annulus. Of these derived measurements, the E/Ea ratio, which represents the early filling velocity over the transmitral inflow (E) divided by the early tissue doppler imaging(TDI)deduced filling velocity over the medial mitral annulus (Ea), appears to have the most prognostic value.(10) A value greater than 15 is associated with a poor prognosis. E/Ea also appears to be relatively load-independent, provided the volume changes during dialysis occur within a narrow range of no more than a litre (52).

2.2.1.3. Pericardial changes

Pericarditis occurs in 15% of CKD patients either before or after the onset of dialysis and is commonly due to uraemia, and to inadequate dialysis(53). In countries, including South Africa, where infectious diseases are common from the relative immunocompromised state of the CKD patient, conditions such as tuberculosis should be considered. There is currently no data examining the incidence of infectious versus uraemic pericardial effusions in the South African context.

Pericardial effusions thus detected represent a management dilemma: it has previously been assumed that more efficient dialysis will largely resolve such effusions. This is often not the case, and there are small studies and case reports to suggest that early

pericardiocentesis may be required to prevent future haemodynamic disturbances and cardiac tamponade(54).

2.2.1.4. Valvular changes on echocardiography

Annular calcification seen in routine echocardiography of the elderly may be seen as an incidental, innocuous and age-related change. But, in the setting of CKD, these changes can be seen as dystrophic calcification, as part of the associated abnormalities in calcium and phosphate metabolism (55) and has prognostic significance. In a study of 192 patients with CKD, valvular calcification of the aortic, mitral or both valves was present in 32% of patients (56). After a mean follow up of 18 months, the mortality rate was 22% versus 3% in those patients with and without valvular calcification respectively (10, 56).

2.2.1.5. Systolic Dysfunction and the problem of Ejection Fraction measurements

The echocardiographic study conducted by Foley et al. reported that the incidence of systolic dysfunction as measured by ejection fraction was 15%(8). Other authors have reported similar findings (7, 10).

However, the accurate measurement of systolic function in CKD represents a unique challenge because of the variable load changes in dialysis. In using Ejection Fraction (EF) as a measure of such function, these difficulties are apparent.

There are two commonly used ways in which EF is calculated in echocardiography; firstly, using the fractional shortening method which uses the internal end diastolic and end systolic diameters of the left ventricle; and secondly, the Modified Simpson's biplanar

method which measures the end diastolic and end systolic volumes of the left ventricle. Both make the assumption the ventricle is a perfect globular structure; secondly, because they are dependent on the dimensions and volumes at the time of measurement, they are dependent on the load changes before and after dialysis.

Following Starling's Law, it would therefore dictate that if preload were increased as it would be before dialysis, the EF would increase, and conversely as preload decreases after dialysis, so too would the EF.

Afterload considerations would also have to be taken into account when measuring EF, with increased afterload decreasing EF and decreasing afterload improving EF.

If one could reliably account for the variable changes during dialysis with both preload and afterload changes, it would be possible to take these into account to measure EF. However, in CKD, uraemic metabolites are negatively inotropic; EF might be expected to improve after dialysis with the removal of these toxins which would offset the Starling Effect.

These concepts were illustrated in a well-designed study by Nixon et al.(57). In this study the same group of patients were echoed under three sets of conditions during their usual dialysis days: 1) ultrafiltration without haemodialysis; 2) haemodialysis without ultrafiltration; and 3) haemodialysis with ultrafiltration.

In the first group, EF diminished as predicted by Starling with the decreased preload **fig.2**; in the second group, haemodialysis reduced toxic metabolites without reducing load resulting in an improved EF **fig. 3**; and in the final group with a reduction in load and toxins, EF remained much the same with only a slight increase in EF **fig.4**.

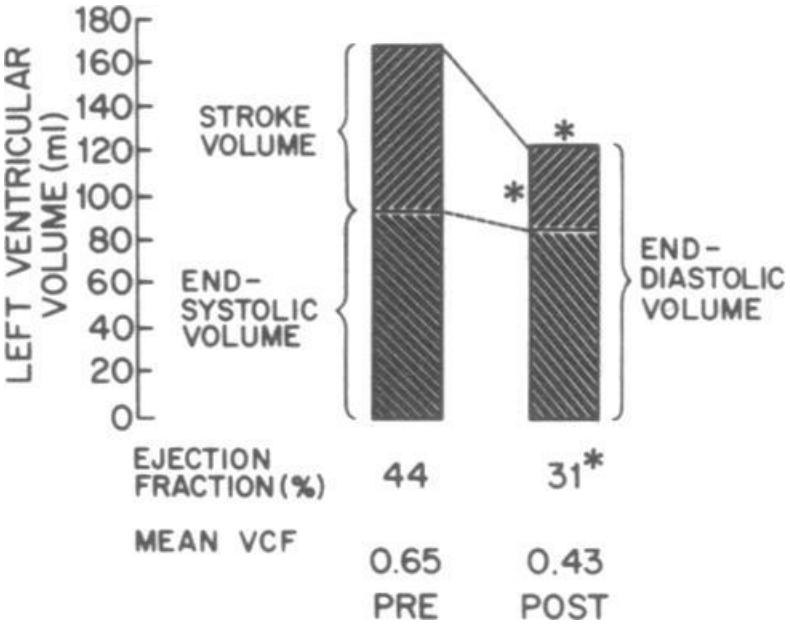


Figure 2. Patients ultrafiltrated without dialysis. EF is significantly decreased. (Reproduced with permission of the American Society for Clinical Investigation.)

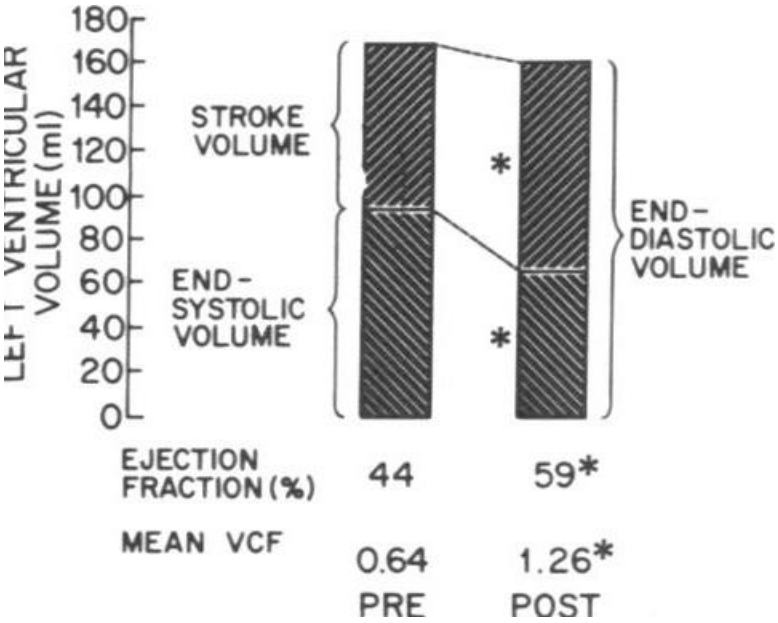


Figure 3. Patients receiving haemodialysis without ultrafiltration. Ejection fraction increased from 44% to 59%. Nixon et. al (J Clin Invest. 1983; 71(2):377-84.) (Reproduced with permission of the American Society for Clinical Investigation.)

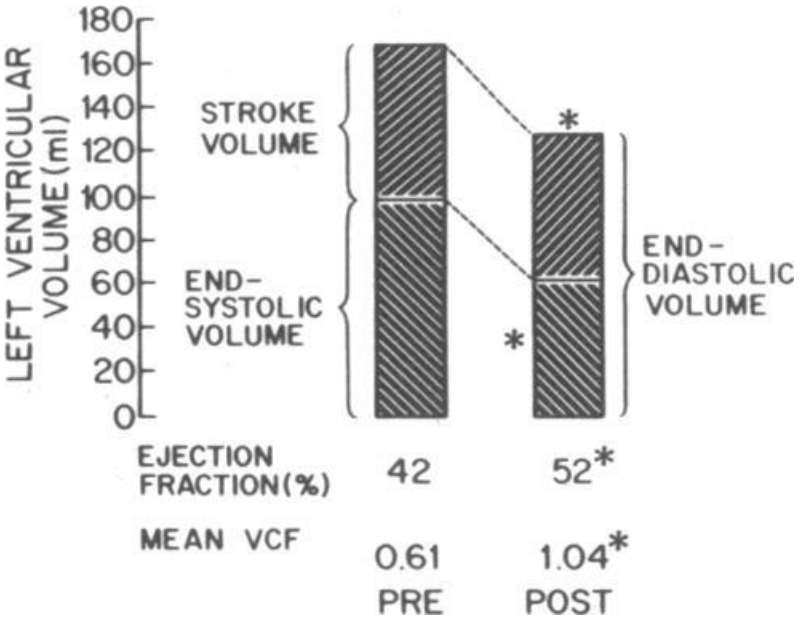


Figure 4. Patients receiving haemodialysis with ultrafiltration. EF increases but less than group 2. Nixon et. al (J Clin Invest. 1983; 71(2):377-84.) (Reproduced with permission of the American Society for Clinical Investigation.)

In clinical practice, the interplay of load versus uraemic toxins may be less predictable. Small studies using echocardiography before and after dialysis have demonstrated this (58, 59).

Because of the variable loading changes in CKD on haemodialysis, the search for a relatively load independent measure of systolic function remains the 'holy grail' of cardiac imaging in CKD.

2.2.2. Other Imaging Modalities: MRI, MUGA and SPECT imaging

Magnetic resonance imaging (MRI) has become the gold standard for the assessment of systolic function in patients with CKD(6). It has the advantage over conventional echocardiography of being able to view the heart in any plane, it offers better definition of the myocardium to blood interface, and it offers accurate and reproducible

measurements of ventricular volumes and ejection fraction(60). However, it is a time consuming and expensive investigation with technical limitations making emergency assessment of patients cumbersome. For these reasons, it is not used routinely in the assessment of CKD patients.

Single-photon emission computed tomography (SPECT) scanning uses a gamma radiation camera to acquire images of radiolabelled tissue using a radioisotope introduced into the body intravenously. It is particularly useful in assessing ischaemic heart disease in using isotopes such as sestamibi which is taken up particularly by the mitochondria- rich myocardium. It is used in measurement of EF by the measurement of radiolabelled red blood cells volumes in diastole and systole. Being a volumetric measurement, it remains load-dependent.

2.2.3. Myocardial Deformation and Strain Imaging

Regardless of the imaging technique used, ejection fraction (EF) as a measure of myocardial function is limited by load; it depends on geometrical assumptions that may not represent true cardiac dimensions or function; and it is insensitive in early cardiac disease. Hence, exploring novel ways to assess heart function such as myocardial deformation may hold much promise.

2.2.3.1 Definitions:

Myocardial deformation describes the changes in shape and motion of the myocardium during systole and diastole. Strain is the deformation of the myocardium under an applied

force and is defined as a change in length or shortening of myocardial fibres relative to its initial length(61) and is used to describe and quantify changes in myocardial deformation(62, 63). It is defined by the following equation:

$$\varepsilon = \frac{L - L^{\circ}}{L^{\circ}} = \Delta L / L^{\circ}$$

Where ε equals strain; L° is the baseline length and L is the instantaneous length. The measurement of strain using the initial length is termed '*Langrangian' strain(63).*
It occurs in four chief directions in the myocardium **fig. 5.**: 1) longitudinal strain which is the change in length in the direction of the long axis of the heart; 2) circumferential strain which is the change in length of myocardial fibres around the circumference of the heart; 3) radial strain which is the lengthening of the myocardial fibres from epicardium to endocardium; and 4) myocardial twist which is the 'wringing' action of the heart. Twist is a composite movement combining longitudinal and circumferential strain. Strain is dimensionless and is expressed as a percentage, except for twist which is measured in degrees. By convention, the shortening that occurs in longitudinal and circumferential strain is assigned a negative value, and the lengthening of radial strain is assigned a positive value.

Measurement of strain has shown good correlation with ejection fraction(64), though not very precisely and may be a surrogate of cardiac function(65).

Strain rate is the change in strain over a given time and is expressed by the equation:

$$Strain\ rate = \delta strain / \delta t$$

It is closely related to dp/dt, the change in pressure over time; and therefore, is an indirect marker for contractility(61). More precisely, peak systolic strain rate, occurs early in systole and may best reflect the intrinsic contractile properties of the myocardium(66).

When strain is calculated from tissue Doppler calculations, length measurements are not made directly. Tissue Doppler is used to calculate strain rate by measuring the instantaneous velocities between two points of interest for a given length:

$$Strain\ Rate = \frac{V_1 - V_2}{d}$$

The integral of the strain rate thus calculated is strain:

$$\int SR\ dt$$

Strain thus derived is termed *'Eulerian' strain(63)* also known as 'natural' strain.

Longitudinal strain has been the most widely assessed form of myocardial deformation. It has been shown to be reduced early in myocardial disease even in patients with preserved EF (66, 67). In comparison, circumferential and radial strain may be compensatory, hence helping in preserving EF in early disease(66).

Langrangian strain and Eulerian strain can be derived from each other and are analogous at low strain (<10%)(66). However, there are small differences in strain values measured depending on the method used to calculate strain and the algorithm used by each individual vendor(66, 68).

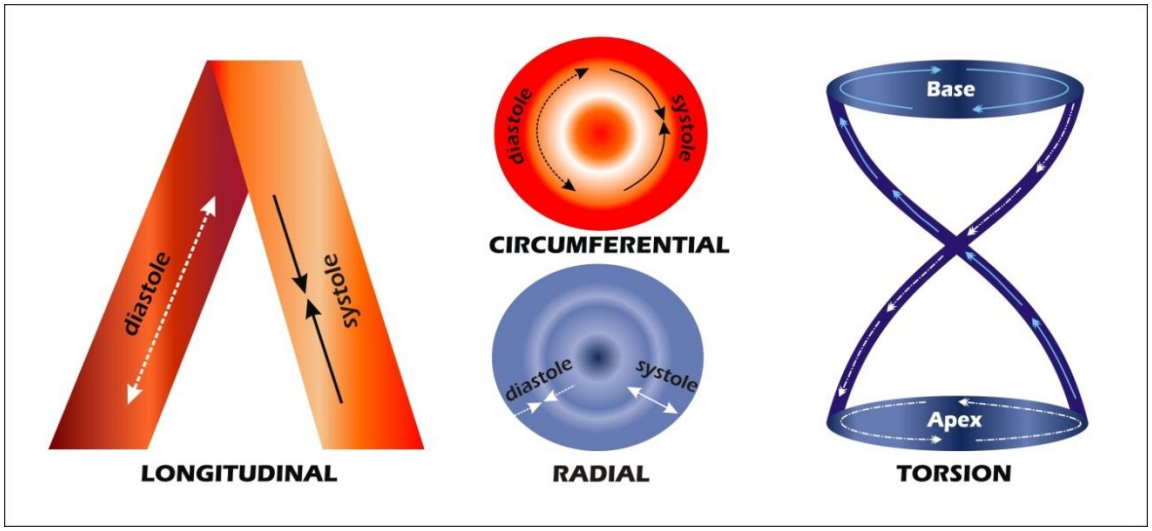


Figure 5. Graphic representation of the principle of myocardial deformation: longitudinal, radial and circumferential, and torsion. The direction of deformation in systole is shown as solid lines and that in diastole is shown in dashed lines.

2.2.3.2. Techniques of measuring strain

Cardiac magnetic resonance imaging (MRI) using myocardial tagging provides a non-invasive method to study myocardial deformation (61, 69). In echocardiography, there are two methods to perform myocardial or strain analysis: 1) tissue Doppler imaging (TDI); and 2) in more recent times the novel technique, speckle tracking echocardiography (STE). Both these techniques have been validated against MRI(70).

2.2.3.2.1. Doppler-based techniques

As mentioned before, strain measurements using tissue Doppler are made indirectly from calculations derived from tissue velocity measurements. Tissue Doppler imaging (TDI) employs ultrasound frequency attuned to myocardial tissue and is used to measure tissue

velocity gradients at specific loci of interest. 'Eulerian' strain is derived from integrals of tissue velocity gradients thus acquired(71).

Tissue Doppler derived strain imaging has been shown in animal studies to correlate well with left ventricular systolic and diastolic function(61).

Though TDI is relatively load-independent, it is not entirely so(71). In addition, its main limitation is its angle dependence, meaning the ultrasound beam needs to be in line with the direction of motion of the myocardial fibres' direction of contraction. This angle of interrogation should not vary by more than 15° to ensure accurate measurement. It is for this reason that TDI imaging has been used primarily for measurement of longitudinal rather than circumferential or radial strain.

2.2.3.2.2. Speckle Tracking Echocardiography

Speckle tracking echocardiography (STE) is a novel method for assessing strain and myocardial deformation which is independent of the angle of the ultrasound beam (71-73). The technique involves the digital labelling of small groups of pixels of myocardial fibres as acquired by echocardiography and designating these small packages or acoustic markers as speckles.

Speckles are of a high resolution and represent 'packages' of 20 to 40 pixels each. They are statistically evenly spaced throughout the myocardium and only require one cardiac frame to track. These speckles can then be accurately tracked by computer software which can be processed off-line long after the images have been acquired. It is therefore not limited to the angle of acquisition as is TDI. However, speckle tracking requires high quality images and acquisition at 50 to 80 frames per second.

Comparisons between TDI versus STE derived strain imaging have shown good correlation between the two techniques(61).

In addition, studies comparing regional left systolic ventricular function measured by MRI versus speckle tracking have shown that STE as a technique has high degree of accuracy with low intra and inter-observer variability compared to the gold standard MRI(74).

2.2.3.3. Left Ventricular Twist

Myocardial twist can be described as the 'wringing 'action of the heart which is the result of the right-handed helical arrangement of sub-epicardial myocardial fibres, and the left handed helix of sub-endocardial fibres **fig. 6** (75-77). Because sub-epicardial fibres on the outside have a wider radius of rotation compared to sub-endocardial fibres, they dominate rotation resulting in a counter-clockwise apical rotation and a clockwise basal rotation **fig.7**. Net twist is the difference between apical and basal rotation and is measured in degrees.

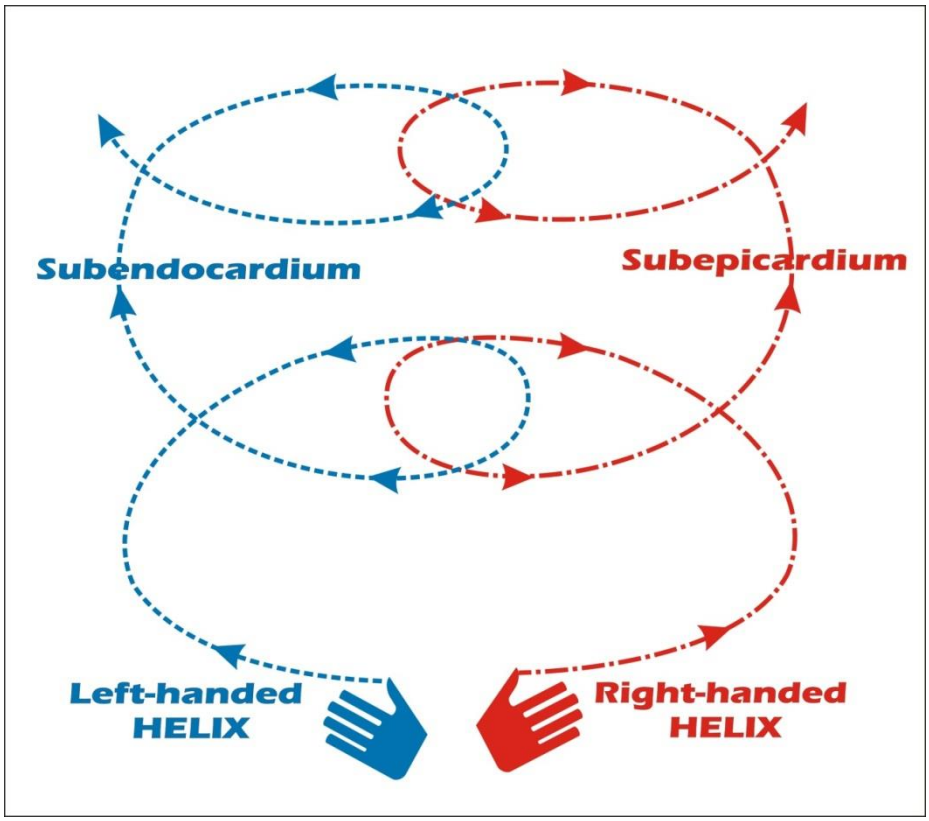


Figure 6. Myocardial fibre orientation and direction. Left handed helical orientation of the sub-endocardium. Right handed helical arrangement of sub-epicardium.

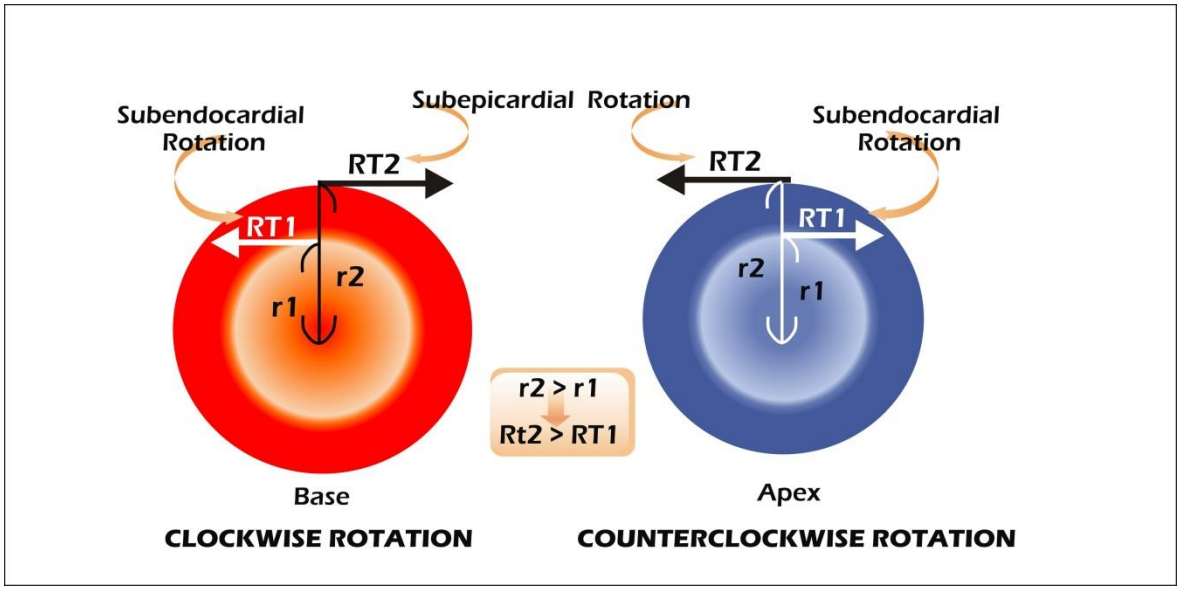


Figure 7. Rotation at the base and apex. Axis of rotation is greater in the sub-epicardium than the sub-endocardium (r2>r1).

2.2.3.4. Global Strain

Global strain reflects the sum of myocardial motion for any given type of strain. It can be calculated manually or by automated software algorithms by averaging all interpretable segments. This minimises the error caused by artefacts in any individual segment. Global longitudinal strain (GLS) and global circumferential strain(GCS) thus measured has been shown to be an analogue of ejection fraction , with good but not exact correlation(66).

A limited number of studies have shown that GLS and GCS offer additional prognostic information beyond ejection fraction alone (65, 66, 78). A study by Stanton et. al which followed up 546 patients who underwent echocardiography to determine baseline ventricular function demonstrated that at EFs of > 35% with no regional wall motion changes, GLS and GCS were independent predictors of future heart failure and death(65).

2.2.3.5. Advantages and disadvantages of strain imaging

Strain imaging offers 4 main advantages(66) over other imaging modalities such as conventional transthoracic echocardiography:

i) Sensitivity: Deformation techniques are able to identify subtle differences in myocardial function allowing for the early detection of pathology. This is because both tissue Doppler and speckle tracking techniques have a narrow enough standard deviation to separate out differences between normal and abnormal myocardium.

ii) Tissue specificity: One of the difficulties of accurately identifying areas of ischaemia in conventional echocardiography arises from the phenomenon of 'tethering'. This refers to the passive movement of an ischaemic region of myocardium which appears falsely to move or be contractile when it is pulled along by surrounding active myocardium.

iii) Relative homogeneity throughout the myocardium: This refers to relatively consistent strain values throughout the myocardium. There are only minor variations in strain from apex to base. Hence, areas of pathology are more readily determined. In comparison, tissue velocities vary more widely.

iv) Physiological correlation: Strain imaging has been found to correlate well with systolic function and can be thought of as analogous to a regional ejection fraction. In addition, strain rate which corresponds well to dp/dt, or the rate of change of pressure over time, is thought to be a surrogate of contractility.

The disadvantages of strain based imaging techniques are that:

i) Tissue Doppler and speckle tracking techniques are computationally complex, requiring complex computer algorithms.

ii) These techniques are user dependent and require a high level of expertise.

iii) Tissue Doppler techniques are highly dependent on angulation of the ultrasound beam to the tissue plane.

iv) In speckle tracking, image quality is essential to accurate measurements.

2.2.3.6. Use of strain imaging in cardiac pathology

Both TDI and STE strain imaging has been investigated in a range of cardiac pathologies which includes ischaemic heart disease, a range of cardiomyopathies, valvular heart disease and pericardial diseases(79).

Strain imaging was first described using TDI derived velocity measurements which were integrated to calculate strain. Because of the angle dependence of TDI, longitudinal strain in the apical view is the easiest to perform as it aligns well with the Doppler scan line. Though some attempts were made to provide an angle correction for the direction of the beam, this is impossible once the direction of motion approaches 90° to the ultrasound beam(80). For this reason, longitudinal strain is the most studied aspect of strain imaging. With the advent of STE imaging in recent years, this angle limitation is no longer an issue with analyses of circumferential, radial and torsional strain (twist) now possible.

In the area of ischaemic heart disease, strain imaging has provided us with additional insights that may not have been gleaned from conventional echocardiography. Ischaemia has been shown to reduce both longitudinal and radial strain (81). The phenomenon of 'post-systolic shortening' (which refers to the observation that the peak of strain occurs from the start of systole till after systole as measured by aortic valve closure) has been seen in animal models (82) and humans subjects (81) with occluded coronary vessels and returns to normal after revascularisation. Speckle tracking echocardiography has proved particularly useful in ischaemic heart disease(67). In traditional echocardiography, determination of ischaemic territory is dependent on observation of regional wall motion changes. With the naked eye, it is difficult to differentiate between active and passive wall motions which STE is easily able to perform by tracking myocardial segments separately(83).

It is in the early detection of myocardial involvement by systemic disease that speckle tracking strain imaging may have its greatest utility. The technique has been tested in a variety of patients with myocardial disorders such as diabetes, scleroderma, amyloidosis, Duchenne's muscular dystrophy, and has been used for early detection of daunorubicin cardiomyopathy(63, 84).

In addition, changes in myocardial deformation have been demonstrated in pericardial diseases which conventional echocardiography may have shown to have normal ejection fractions.

Studies have also suggested that strain imaging and speckle tracking may have a place in assessing cardiac transplant rejection, and to look for ventricular dissynchrony for the optimal utilisation of cardiac resynchronisation therapy(84).

2.2.3.7. Use of strain imaging in chronic kidney disease

Strain imaging provides intriguing possibility in the early detection of cardiac involvement in CKD and may allow the development of more accurate techniques to assess systolic function.

In recent years, a few small studies have emerged investigating strain analysis in CKD patients (58, 59, 85-87). Three of these studies examined strain in patients with CKD and preserved ejection fraction compared to normal controls (85, 87, 88). Edwards et. al. used colour TDI to analyse the longitudinal strain of the septal and lateral walls of the myocardium (88). In comparison, Yan et al.(87) and Liu et. al. (85, 87, 88) used STE to assess longitudinal, circumferential and radial strain. All three studies concluded that in CKD patients longitudinal strain was reduced compared to their controls despite normal

ejection fractions. Furthermore, circumferential and radial strain was also shown to be reduced in the STE studies. However, it was also shown that all three measured parameters of strain improved in patients with CKD on dialysis compared to CKD patients in stages 3, 4 and 5 not yet requiring dialysis(85, 87).

Mendes et al.(59) and Choi et al.(58) explored the effect of load changes during intermittent haemodialysis on both ejection fraction and longitudinal strain before and after a single dialysis session. Mendes et al examined 20 patients before and after dialysis using both TDI and STE. This study showed no significant change in both the EF and global longitudinal strain (EF of 55 ± 9% before dialysis vs. 55 ± 10% after dialysis, p = 0.3; and GLS of -18 ± 4% vs. -17 ± 5%, p = 0.5). They concluded that GLS may be a relatively load independent marker of systolic function. Their explanation of the lack of change in ejection fraction was that 'a reduction in inotropism secondary to lower end diastolic volumes may have been cancelled out by the increased inotropism arising from the removal of cardiotoxic metabolites' (59). In comparison, Choi et al. appeared to draw a different conclusion: that global longitudinal strain is load dependent. Choi et. al examined 21 CKD patients on intermittent haemodialysis (mean age 54 ± 15 years, 17 male with mean ultrafiltration volume 3100 ± 0.9ml) using STE. This study showed no change in EF during dialysis (62 ± 9% vs. 62 ± 8%, p = 0.9) but a significant reduction in GLS (-18.4 ± 2.9% vs. – 16.9 ± 3.2%, p = <0.001).

Closer evaluation of both studies shows that their results may not have been as markedly different. Choi et al. calculated global longitudinal strain in a number of ways: he used apical four chamber, apical two chamber and parasternal long axis views to obtained 16

segments from which GLS is calculated by averaging out these segments; he performed a segmental analysis of longitudinal strain at the apex, mid-myocardium and base of the heart; and finally, he provided an averaged global longitudinal strain in the apical four chamber, apical two chamber and parasternal long axis views. Mendes et. al calculated GLS from an average of the 6 measured segments in the apical four chamber views(59). Examining the value of GLS in Choi's study using the apical four chamber values(-18,0 ± 3.1 % vs. 17.0 ± 3.0%, p = 0.03), the difference, though present, is less marked than the difference in the apical two chamber (-19.4 ± 3.6 % vs., -17.5 ± 3.6%, p <0.001) and long axis views (-17.9 ± 3.1% vs. -16.9 ± 3.2 %, p<0.001)(58). It is probable that, though GLS has been validated in previous studies to be a good correlate for left ventricular systolic function(78), it is (to varying degrees) load dependent(66).

Strain has also been used to evaluate CAD in patients with CKD. In a study by Liu et al., STE was performed on 102 haemodialysis patients with and without CAD. GLS, circumferential strain and segmental strain was shown to be reduced in patients with CAD (86). This was shown despite biomarkers such as Troponin T, highly sensitive CRP, Interleukin 6 and 18 not being significantly different between the two groups(86).

These studies, though limited in numbers, suggest that strain imaging may be of value in the early detection of myocardial pathology in the CKD patient.

2.2.4. Studies of Cardiac Function in Black African populations

Though the study of cardiac function and pathology in CKD continues to evolve with the latest advances in imaging, there remains a paucity of data from the African continent. In 2009, a retrospective study was conducted by Luyckx et al. evaluated an African CKD population of 202 patients at Chris Hani Baragwanath Hospital on either peritoneal or haemodialysis(89). These patients had a low incidence of pre-existing cardiac disease and were of a younger age then reported in western literature: the mean age of patients was 41.7 ± 7 years with a median follow up of 28 months. During this time, 39 patients died (19%) of the patients died; 41% of these were related to sepsis or tuberculosis, 12.8% were access related (non-infectious deaths), 12.8% were a result of non-compliance and a uraemic death, 10.2 % of deaths were from cardiovascular causes, and 23.1% were of miscellaneous causes (which included myeloma, bleeds, bowel obstruction and unknown aetiologies). The main findings of this study were that though left ventricular hypertrophy was common, the incidence of systolic dysfunction was low at 9.9%, compared to other studies; and patients died at a younger age of primarily infectious diseases.

This study had many limitations: being a retrospective study, with selection bias towards a younger population as resource limitations excluded older patients from being on the dialysis programme. The disproportionate number of deaths from infectious diseases including tuberculosis which is endemic in this population may have masked underlying cardiac pathology which may have become manifest later. More prospective studies are required in this country and throughout Africa to provide a true reflection of the profile of cardiac disease in local CKD populations.

2.3. Conclusion

This review has provided some insights into the challenges that cardiac disease represents to the CKD patient. The variable load and metabolic changes in CKD patients on dialysis makes accurate assessment with the available forms of cardiac imaging challenging with the frequently used measure, ejection fraction, a volume and therefore a load dependent measure. Though cardiac MRI has become the gold standard for assessing myocardial function in CKD, echocardiography remains the most practical and commonly used imaging modality. Therefore, STE provided us with an opportunity to enhance the use of echocardiography in renal patients.

STE strain imaging may add to our understanding of cardiac changes in CKD, and represents an attractive tool for early detection of subtle cardiac involvement in kidney disease.

Furthermore, studies clarifying the cardiac disease burden in Black African patients with chronic kidney disease remain scarce.
This thesis hopes to address these issues.

3. HYPOTHESIS:

The hypothesis of this study was that global longitudinal, radial, circumferential strain and left ventricular twist as measured by speckled tracking echocardiography are not significantly affected by haemodialysis in patients with chronic kidney disease.

4. **MATERIAL AND METHODS**

4.1. AIMS

The aim of this prospective, cross-sectional, single-centre, pilot study was to determine the utility of myocardial deformation imaging in CKD before and after dialysis.
This study was designed to test the hypothesis that myocardial deformation is relatively load-independent and would not change significantly before and after dialysis.
Specifically, the objectives of this research were:

1) To determine whether there are significant changes in the 4 chief components of myocardial deformation (longitudinal; circumferential; radial and rotational strain) as a result of dialysis in CKD patients.
2) To determine whether expected changes in preload as determined by changes in left ventricular volumes (left ventricular end diastolic volume (LVEDV); and left atrial volume (LAV)) affects myocardial deformation.
3) To determine whether possible changes in afterload as determined by surrogate measures (mean arterial pressure (MAP) and pulse pressure over stroke volume ratio (PP/SV) (a marker of arterial stiffness) impact on such changes in myocardial deformation.

4) To determine the effects of these load changes on myocardial deformation compared to ejection fraction.
5) To compare myocardial deformation in CKD patients to normal controls to determine whether strain imaging might detect early pathological changes in cardiac function.

4.2. Study population

This study was conducted at the Chris Hani Baragwanath Hospital Renal Unit in Soweto, Johannesburg. Volunteers were screened and recruited from patients receiving maintenance haemodialysis three times a week during the period from November 2010 to February 2011.

The inclusion criteria were:

1) Age between 20 to 65 years
2) African descent
3) End stage kidney disease on chronic haemodialysis

The exclusion criteria were:

1) Known pre-existing cardiac disease ascertained on questionnaire, including
    a. Heart failure
    b. Documented ischaemic heart disease
    c. Arrhythmias including atrial fibrillation
    d. Valvular heart disease
2) Poor echocardiography windows as determined during a screening echocardiogram which precluded speckle tracking

Volunteers from a total of seventy CKD patients in the haemodialysis unit were thus screened; thirty three patients met the criteria for the study. Written consent was obtained and each patient was asked to come to the Core Echocardiography Laboratory at Chris Hani Baragwanath Hospital on a dialysis day.

A clinical history was obtained from CKD patients with a relevant physical examination (blood pressure, weight, height, volume status, and cardiac examination). Comprehensive transthoracic echocardiography was performed on each subject.

Seven patients were excluded after initial echocardiography as more than 2 segments in any given view failed to yield speckle tracking data precluding any meaningful analysis of strain.

Therefore, there were 26 CKD patients that made up the final study group.

Twenty six age and gender matched healthy volunteers were recruited as a control group. They were part of a cohort that were recruited as part of an on-going initiative to establish normative data on myocardial deformation in individuals of African descent and has recently been published(90).

Ethical approval for this study was obtained from the University of the Witwatersrand's Ethics Committee (No. M10510).

4.3. Haemodialysis

All CKD patients attended the Chris Hani Baragwanath Hospital haemodialysis unit three times a week for chronic haemodialysis (HD). They were on HD for an average of 4 hours with a mean ultrafiltration volume of 2.24 ± 0.9 litres.

Patients were dialysed using the Fresenius FX dialysers which are high flux, with greater clearance and are considered more biocompatible. Most patients were dialysed on the FX 80 dialysers, though the range of dialysers used were FX 60, FX 80 and FX 100 according to the patient's weight.

The recombinant erythropoietin, Recormin, was used to maintain haemoglobin levels at a target of 11 to 12 g/dl in keeping with KDIGO guidelines at the time. An average of 12000 units was given per patient per week.

The dialysate used during dialysis was bicarbonate based; bicarbonate is considered safer with gentler effects on electrolytes, acid-base status with lesser side effects and fewer anaphylactic reactions.

4.4. Echocardiography

Both CKD patients and healthy volunteers had echocardiography at baseline. Echocardiograms were performed within an hour before and after a single haemodialysis session.

According to a standardised protocol used by our institution (90-92), comprehensive echocardiographic examination was performed in the lateral decubitus position using a commercially available system (iE33 xMATRIX, Philips Healthcare, Andover, MA, USA) equipped with an S5-1 transducer (frequency transmitted 1.7MHz, frequency received 3.4MHz). Measurements obtained were averaged from three heartbeats. All data was transferred to an Xcelera workstation (Phillips Healthcare) for offline analysis.

Chamber size measurements and function were performed according to the American Society of Echocardiography (ASE) chamber quantification guidelines of 2006(46) and the ASE guidelines on right heart evaluation in 2010(93). ASE guidelines on valvular regurgitation were used to analyse severity of mitral and tricuspid regurgitation (94). Ejection Fraction (EF) was calculated using LV volumes by the modified biplane Simpson's rule in keeping with guidelines (46). The mitral-inflow pattern were used to measure the peak early (E) and late (A) filling velocities, the E/A ratio and the E-velocity deceleration. End-expiratory tissue Doppler views were obtained of the inferoseptal side of the mitral annulus in the pulsed wave mode. The angle between the Doppler beam and the longitudinal motion of the structure were kept to a minimum in order to obtain the highest wall tissue velocities with the spectral pulse-wave Doppler velocity adjusted to an appropriate gain.

Timing intervals of the R-wave on electrocardiogram (ECG) to the aortic valve opening and closing; and the R-wave on ECG to the mitral valve opening and closing were measured using pulsed wave Doppler over the outflow and inflow tracts respectively.

Left ventricular mass (LVM) was calculated using the following formula (93, 95):

$LVM = 0.8 \times (1.04[(LVIDd + PWTd + SWTd^3 – (LVIDd)^3]) + 0.6g$

Where LVIDd is the left ventricular diameter at end diastole; PWTd is the posterior wall thickness at end diastole; and SWTd is the septal wall thickness at end diastole.

Relative wall thickness (RWT) was calculated as follows (46, 95): (2 x PWTd)/LVIDd.

Using the derived calculations: concentric hypertrophy was defined as RWT > 0.42 and eccentric hypertrophy as RWT < 0.42 (with LVMI in females > 95g/m^2 and LVMI > 115 g/m^2 in males in both types of hypertrophy)(95).

4.4.1. Markers for preload and afterload

LVEDV was taken as representative of preload. Stroke volume was calculated according to the formula: SV = LVEDV - LVESV. Pulse pressure over stroke volume (PP/SV) has previously been evaluated as a surrogate of arterial stiffness (96, 97) that takes into account the contributions of systemic vascular resistance and ventricular compliance to afterload (98). The PP/SV ratio has previously been validated and used in trials such as the LIFE study (99). Pulse pressure was calculated with the formula: PP= SBP- DBP. Mean arterial pressure (MAP) was used as an indirect marker for afterload as it is a major contributor to systemic vascular resistance and was calculated as follows: MAP = 1/3 SBP +2/3 DBP.

4.4.2. Speckle Tracking Analysis

For optimal speckle tracking, echocardiographic images were obtained at a frame rate of 50 to 80 frames per second in sinus rhythm with less than 10% heart rate variability(75). Standard echocardiographic images were obtained in: 1) the apical 4 chamber view for longitudinal strain analysis; 2) apical and basal short axis views for twist analysis; and 3) mid-ventricular short axis views for circumferential and radial strain analysis.
Echocardiographic data acquired were analysed offline. Images were reviewed for quality control: an independent cardiologist (Dr FFE Peters) experienced in speckle tracking echocardiography (STE) accessed all images acquired and assess their suitability for speckle tracking using QLAB Advanced Quantification software (Version 8.0, Philips Healthcare).
For STE, basal images were obtained in the parasternal short axis at the level of the mitral valve showing the tips of leaflets with the most circular image possible. Mid-ventricular short axis views were acquired at the level of medial and lateral papillary muscles. Apical images were acquired by moving the transducer one or two spaces caudally using the method described by Van Dalen(100).

4.4.3 Global Peak Longitudinal Strain (GPLS)

Images acquired in the apical 4 chamber view at the apex in end-expiration were used for speckle tracking of longitudinal strain.
Four chamber views were divided by speckle tracking software into the following segments **fig.8**: 1) apicoseptal; 2) apicolateral; 3) midseptal; 4) midlateral; 5) basoseptal;

and 6) basolateral segments. Global peak longitudinal strain was calculated as the average peak strain of the above segments.

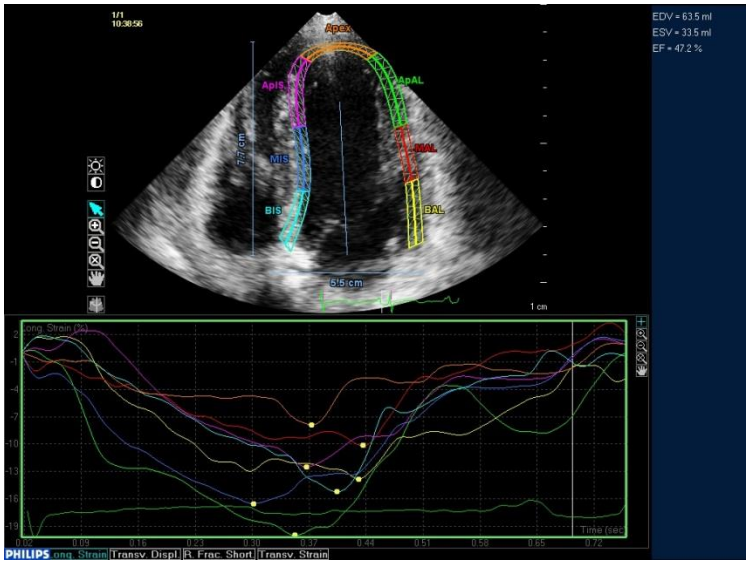


Figure 8. Apical 4 chamber (AP4C) view showing speckle tracking. Longitudinal segments are divided into segments by an automated algorithm. Each coloured wave below represents the strain of one segment tracked. The Y-axis is a percentage of lengthening and is from 0 to -20. The X-axis is time in seconds.

4.4.4. Global Peak Circumferential Strain (GPCS) and Global Peak Radial Strain (GPRS)

Mid-ventricular short axis (MSAX) views were acquired by ensuring the most circular views possible which included the medial and lateral papillary muscles. Images obtained at the MSAX level allow for optimal measurement of radial and circumferential strain.

The QLab 8 software divides MSAX images acquired into six segments **figs. 9 and 10.** : 1) Anterior; 2) posterior; 3) anterolateral; 4) anteromedial; 5) posterolateral; and 6) posteromedial.

Global peak circumferential strain (GPCS) and global peak radial strain (GPRS) were calculated from averages of the six respective segments.

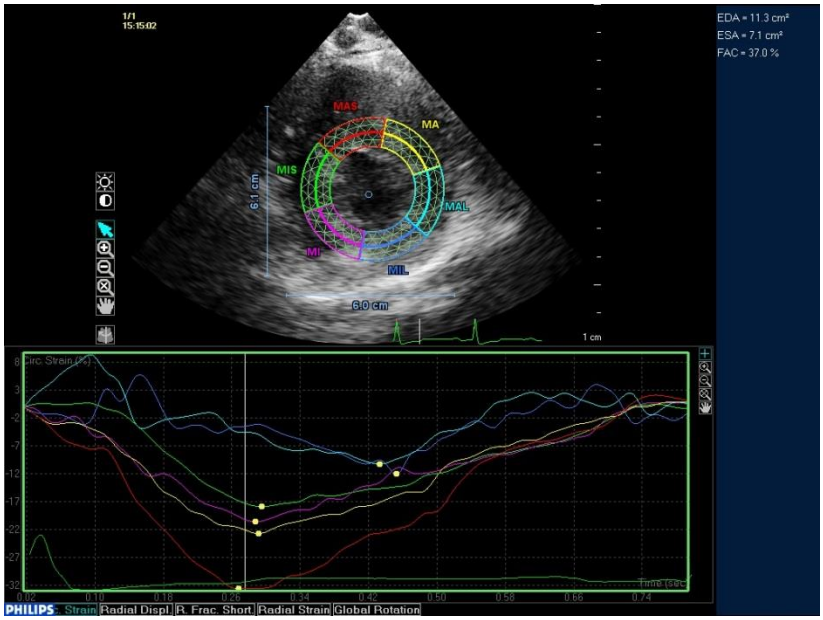


Figure 9. Mid-ventricular short axis (SAX) view. Cirumference is divided into 6 segments by program software. Strain cuves are below a coloured to represent segments. The Y-axis is a percentage of lengthening and is from 0 to -32. The X-axis is time in seconds.

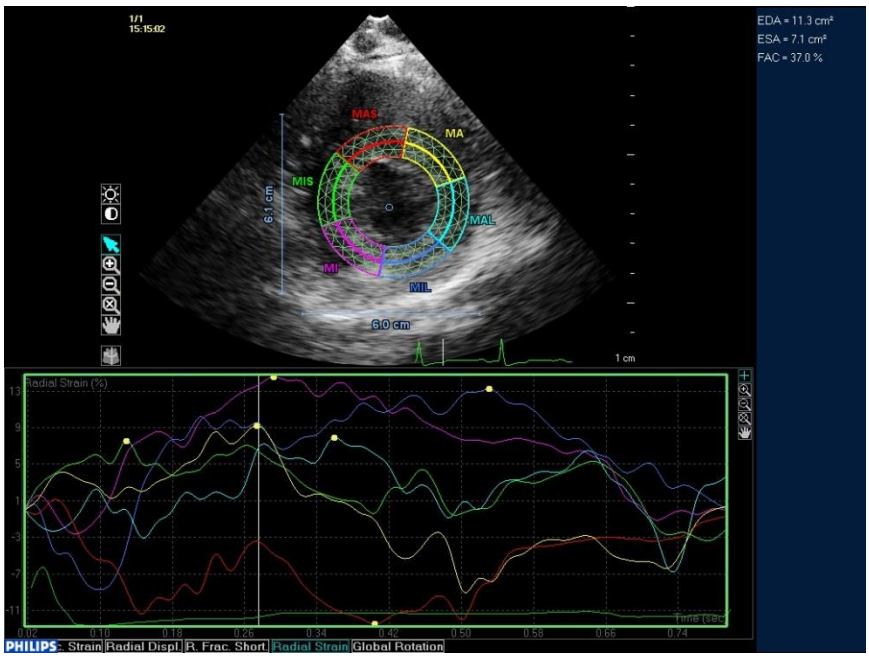


Figure 10. Mid- ventricular SAX view showing segmental division of heart circumference for tracking of radial strain. Note that unlike circumferential strain, values are positive representing shortening. The Y-axis is a percentage of shortening and is from 13 to -11. The X-axis is time in seconds.

Manual adjustments of tracking points were made in the region of interest if segments did not track well. Data was accepted if no more than two segments failed to track per view.

4.4.5. Left Ventricular Twist

In the basal parasternal short axis view, six tracking points were placed on the myocardium on an end-diastolic diameter as determined by an automated algorithm determined by the software. Care was taken to avoid the pericardium. Tracking points were 60° apart to complete the circumference of the left ventricle (101), and could be repositioned to improve tracking, providing any point was not moved more than 30°. At the apex, the automated software placed tracking points from endocardium to epicardium. Once tracking points were placed, these points were tracked by the programme.

By ASE convention, counter-clockwise viewed from the apex is taken as positive and clockwise rotation at the base is taken as negative (102). Apical rotation was taken as the peak systolic rotation with end-systole taken at the point of aortic valve closure; **fig. 11**. Basal rotation was taken at a point isochronous to peak apical rotation following a convention in our core echocardiography laboratory and has been previously published; **fig. 12**. (90-92, 101).

Net twist was calculated as the difference between peak apical rotation and isochronous basal rotation (90-92, 101).

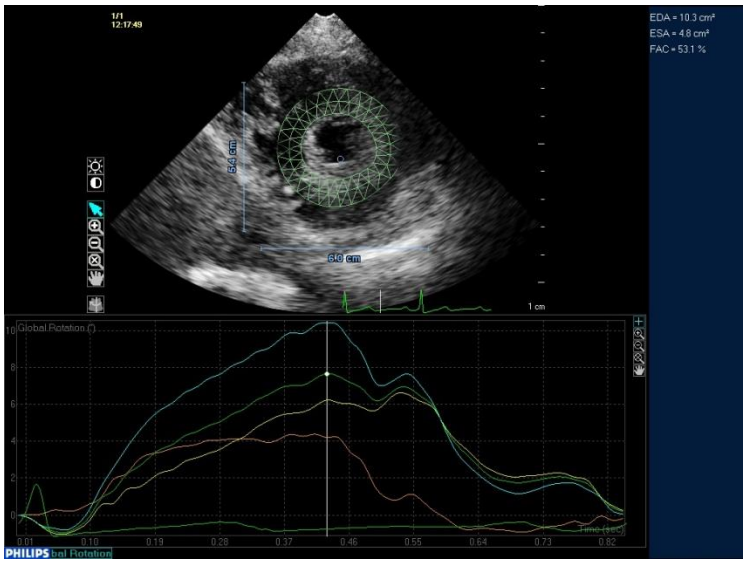


Figure 11. SAX view through the apex. By convention curves are given a positive value for counter-clockwise rotation. The green curve is Global Rotation. The blue curve is sub-epicardial strain and the yellow curve is sub-endocardial strain. The Y-axis is in degrees of rotation and is from 0 to 10 degrees. The X-axis is time in seconds.

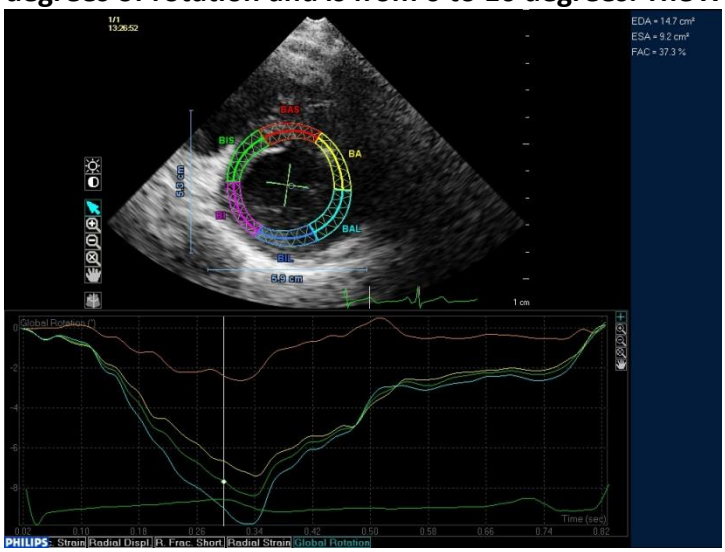


Figure 12. Basal Rotation in the SAX view. Curves are negative reflecting clockwise rotation. Value is not taken at the peak but a time equal (isochronous) to the peak apical rotation so that instantaneous twist can be calculated. . The Y-axis is in degrees of rotation and is from 0 to -8 degrees. The X-axis is time in seconds.

4.4.6. Inter and intra-observer variability

Two independent physicians performed speckle tracking analysis on 10 randomly selected echocardiographic examinations. Values obtained by the author of this dissertation during offline analysis, were compared against the values obtained by an independent physician, experienced in speckle tracking echocardiography, for determination of inter-observer variation. Repeat analysis performed by the author at least a week after origin measurements were used to calculate intra-observer variation

Global Peak Longitudinal Strain (GPLS)

The mean inter-observer variability for GPLS in renal patients pre-dialysis was 4.1 %; and post-dialysis 4.2%.

The mean intra-observer variability in renal patients pre-dialysis was 2.5%; and post dialysis was 5.0%.

Global Peak Circumferential Strain (GPCS)

The mean inter-observer variability for GPCS in renal patients pre-dialysis was 7.7 %; and post-dialysis 1.9%.

The mean intra-observer variability in renal patients pre-dialysis was 4.3%; and post dialysis was 3.6%.

Global Peak Radial Strain (GPRS)

The mean inter-observer variability for GPRS in renal patients pre-dialysis was 12.0 %; and post-dialysis 29.0%.

The mean intra-observer variability in renal patients pre-dialysis was 6.0%; and post dialysis was 25.0%.

Rotation and twist:

The mean inter-observer variability (between the two physicians' measurements) in renal patients pre-dialysis was 3.67 %; and post-dialysis 3.7%. The mean intra-observer variation pre-dialysis was 2.76%; and post-dialysis 3.72%.

Both inter-observer and intra-observer variability for global peak longitudinal strain (GPLS) and twist measurements were ≤ 5%. For global circumferential strain inter-observer and intra-observer variability was < 8%. But the variability for global peak radial strain showed a wide variability of up to 29%.

5. Statistical Analysis

All data captured was recorded on Excel.

Data was analysed using the Statistica version 11 (Statsoft; Tulsa, Oklahoma, USA) program. Results were expressed as means with standard deviations or medians for non-normal distribution or frequencies, and percentages for categorical variables. Correlation of variables was assessed by use of the Spearman's correlation co-efficient.

Comparison between patient data and controls

All normally distributed echocardiographic and clinical data were analysed using a paired t test for each set of dialysis patients before and after dialysis:

i. Ejection fraction in % measured by the modified Simpson's technique
ii. Blood pressure measurements before and after dialysis in mmHg
iii. Change in Weight/ Mass in kilograms
iv. Echocardiographic measurement (pre and post dialysis)for :
    a. Left ventricular end systolic (LVESV) and end diastolic (LVEDV) volumes measured in cubic centimetres
    b. Left ventricular end systolic (LVESD) and diastolic(LVEDD) diameters in millimetres
    c. Left ventricular mass(LVM) in grams
    d. Left atrial volume index (LAVI) as ml/m^2

To assess differences between the control groups vs. pre-dialysis patients and control vs. post-dialysis patients, the Mann Whitney test for non-normally distributed, independent variables was used for the following:

i. Global Longitudinal strain (GLS) by speckled tracking analysis measured as a % change.
ii. Global Circumferential strain (GCS) measurements in %
iii. Global Radial strain(GRS) measurements in %
iv. Left Ventricular twist in degrees.

Pre and post dialysis data

Pre and post-dialysis comparisons were performed with the Wilcoxon matched paired test for dependent, non- normally distributed variables, viz., all strain measurements.

Significance was assumed at two-sided values of $p < 0.05$.

6. **RESULTS:**

Dialysis patients had underlying anaemia with mean haemoglobin of 9.9 ± 2.3 g/dl.

Patients were on dialysis for a mean time of 6.7 ± 3.4 years.

The patients appeared to be well dialysed, with good control of metabolic parameters. Calcium levels were within normal limits with mean of 2.3 ± 0.3 mmol/l (n = 2.2 to 2.6 mmol/L) and only moderately increased PTH levels of 66 ± 68 pg/ml (n = 11 to 54 pg/ml). Phosphate levels and Calcium x Phosphate levels were 1.33 ± 0.5 mmol/l (n = 0.8 to 1.5 mmol/L) and 37.6 ± 15.5 g^2dl^2 (n = 21.4 g^2dl^2 to 41.4 g^2dl^2) and within the target ranges for this population.

6.1. Baseline Characteristics

Control vs. Renal patients before dialysis

The mean age of the control group was 44 ± 11.4 years vs. 43.4 ± 12.2 years in the renal group (p=0.81); there were 46% males in each group.

Body weight (66.2 ± 8.5 kg vs. 65.2 ± 12.9 kg); BMI (24.7 ± 2.5 kg/m^2 vs. 24.2 ± 4 kg/m^2) and BSA (1.73 ± 0.1 m^2 vs. 1.72 ± 0.2 m^2) was similar between groups. **table 1.**

In contrast, there were significant differences in systolic blood pressure (122.7 ± 5.1 mmHg vs. 151.8 ± 17.6 mmHg, P <0.01); diastolic blood pressure (75.5 ± 10.2 mmHg vs.

90.1 ± 14.1 mmHg, P < 0.01); and heart rate (70.3 ± 11.9 beats/min vs. 81.8 ± 11.9; P<0.01) between the control and dialysis groups respectively. **table 1**.

Eighty one percent of the renal group were hypertensive and 8% were diabetic.

Renal patients before and after dialysis

During dialysis, patients were ultra-filtrated a mean of 2.24 ± 0.9 litres with a mean change in weight of 2.18 ±1kg. As a result, there was a significant difference in pre and post dialysis weights. **table 1.**

No statistically significant differences between systolic, diastolic, mean arterial pressure and heart rate were seen comparing pre- and post-dialysis data.

Table 1. Clinical Characteristics of patients and controls

	Control (n=26)	**Pre-dialysis (n=26)**	**Post-dialysis (n=26)**
Mean age (years)	44.0 ± 11.4	43.4 ± 12.2	-
Male Gender (%)	12(46%)	12 (46%)	-
Height (cm)	163.6 ±8.9	164.0 ± 9.6	-
Weight (kg)	66.2± 8.5	65.2 ± 12.9	63.0 ± 12.6†
Change in weight (kg)	-	-	2.2 ±1.0
Haemoglobin (g/dl)	-	9.9±2.3	-
Heart Rate (beats/min)	70.3 ±11.9	81.8 ± 11.9*	89.7 ± 18.3
Body Mass Index (BMI) (kg/m^2)	24.7 ±2.5	24.2 ± 4.0	-
Body Surface Area (BSA) (m^2)	1.7 ± 0.1	1.7 ± 0.2	-
Diabetes Mellitus (%)	0	2 (8%)*	-
Hypertension (%)	0	22 (81%)*	-
Systolic blood pressure (mmHg)	122.7 ± 5.1	151.8 ± 17.6*	145.0 ± 24.5
Diastolic blood pressure (mmHg)	75.5± 10.2	90.1 ± 14.1*	88.4 ± 16.5
Mean Arterial Pressure (mmHg)	91.2 ±7.4	110.6 ±13.7*	107.4 ±18.0
Pulse Pressure (mmHg)	47.2 ±10.3	61.7 ±14.4*	56.6 ±16.3
Amount ultrafiltrated (L)	-	-	2.2 ±0.9
Years on dialysis	-	6.7 ±3.4	-
Corrected Calcium (mmol/L)	-	2.3±0.3	-
Corrected Calcium (g/dl)		9.2±1.3	-
Phosphate (mmol/L)	-	1.3±0.5	-
Calcium X Phosphate Product (g^2/dl^2)	-	37.6±15.5	-
Parathyroid hormone level (pg/ml)	-	66±68	-

*p- value <0.05 control vs. pre-dialysis group (Mann Whitney test), †p- value <0.05 pre vs. post-dialysis group (Wilcoxon Rank Sum test)

6.2. Echocardiographic characteristics:

Control vs. Renal patients

There were differences in echocardiographically measured dimensions between normal controls and renal patients before dialysis with left ventricular diastolic volume LVEDV (71 ± 9.8 ml vs. 97.9 ± 39.2 ml; $p < 0.01$); and end systolic diameter LVESD (28.8 ± 0.4 mm vs. 32 ± 0.64; $p < 0.05$). **table 2**.

The following differences were seen in the indices of filling pressure: E/Ea (mean 9.8 ± 2.4 vs. 15.23 ± 5.22; $p < 0.05$) and left atrial volume index (LAVI) (25.8 ± 5.6 ml/m^2 vs. 33.4 ± 15.2 ml/m^2; $p < 0.01$). **table 2.**

There was concentric left ventricular hypertrophy amongst renal patients with IVSD 14.1 ± 0.3 mm; RWT 0.6 ± 0.12; and LVMI 156.1 ± 61.9 g/m^2. Left ventricular hypertrophy was present in 88% of renal patients (23 of 26 patients). In those patients with hypertrophy, 96% (22 patients) were concentric in pattern and 4% had eccentric hypertrophy (1 patient).

Ejection fraction (EF) and the pulse pressure over stroke volume ratio (PP/SV), which is a surrogate marker for aortic compliance therefore afterload (98), were similar in the two groups (1.31 ± 0.8 vs. 1.39 ± 0.9). **table 2**.

Renal patients before and after dialysis

There was a significant change in volume in renal patients pre and post dialysis with LVEDV (97.9 ± 39.2 ml vs. 83.5 ± 23.9 ml; $p = 0.02$); LVESV (41.1± 23.7 ml vs. 35.2 ± 20.3; p

< 0.05); and in indices of filling pressure with LAVI (33.4 ±25.2ml/m^2 vs. 27.8 ±15.6 ml/m^2; p <0.05) and E/Ea ratio (15.2 ±5.2 vs. 13.0±5.8; p < 0.05). (table 2.)

There was a significant increase in EF in the renal cohort after dialysis (58.8 ± 13.7 % vs. 61.2 ± 13.6 %; p = 0.02). However, the pulse pressure to stroke volume ratio did not change (1.4 ± 0.9 vs. 1.3 ± 0.8; p = 0.29).

Table 2. Echocardiographic Characteristics

	Control (n=26)	**Pre-dialysis (n=26)**	**Post-dialysis (n=26)**
LV end-diastolic volume (ml)	71.0 ± 9.8	97.9 ±39.2*	83.5 ± 23.9†
LV end-systolic volume (ml)	30.6 ± 7.6	41.1 ±23.7	35.2 ±20.3†
Stroke Volume (ml)	40.5 ± 10.2	57.4 ±28.3*	49.3±16.5
LV end-diastolic diameter (mm)	44.9 ± 0.3	45.8 ± 0.7	45.3 ± 0.6
LV end-systolic diameter (mm)	28.8 ± 0.4	32 .0 ±0.6*	29.7 ± 0.6
Interventricular septal diameter (mm)	10.0 ± 0.2	14.1 ± 0.3*	14.0 ±0.3
Posterior wall thickness (mm)	9 .0 ± 0.1	13.5 ± 0.3*	13.2 ± 0.3
Relative wall thickness (mm)	0.4 ±0.04	0.6 ±0.1*	0.6 ±0.1
Ejection Fraction (%)	61.7 ± 6.2	58.8 ± 13.7	61.2 ±13.6†
LV mass index (g/m^2)	84.5 ±18.9	156.1 ±61.9*	152.7±62
Left Atrial Vol. Index(ml)	25.8 ±5.6	33.4 ±15.2 *	27.8±15.6†
Mitral E/A (ratio)	1.2 ± 0.4	1.1 ± 0.4	1.1 ± 0.7
E/Ea (ratio)	9.8 ± 2.4	15.2± 5.2*	13.0± 5.8†
Pulse Pressure/Stroke Vol (mmHg/ml)	1.3 ±0.8	1.4 ±0.9	1.3 ± 0.8

*p value <0.05 control vs. pre-dialysis group (Mann Whitney test), †p value <0.05 pre vs. post - dialysis group (Wilcoxon Rank Sum test)

6.3. Global longitudinal, circumferential and radial strain characteristics.

Controls vs. Renal patients before dialysis

Global peak longitudinal strain (GPLS) was not significantly different between normal controls and renal patients at baseline (-16.0 ± 2.7 vs. -14.2 ± 3.0, p = 0.08). Similarly, global peak circumferential strain (GPCS) was similar: (-16.0 ± 2.9 vs. -17.4 ± 4.8, p = 0.25). **table 3**.

Global peak radial strain (GPRS) was found to be significantly higher in normal control subjects compared to pre-dialysis renal patients. (27.9 ± 1.4 vs. 10.8 ± 6.4; p<0.01).**table 3.**

Renal patients before and after dialysis

GPLS did not differ significantly before and after dialysis: (-14.2 ± 3.0 vs. -13.4 ± 3.0' p>0.05); neither did GPCS (-17.4 ± 4.8 vs. -16.9 ± 5.1, p>0.05); nor GPRS (10.8 ± 6.4 vs. 19.9 ± 17.6, p>0.05). **table 3**.

Table 3. Strain characteristics

	Control (n=26)	**Pre-dialysis (n=26)**	**Post-dialysis (n=26)**
Global Longitudinal Strain	-16.0 (±2.7)	-14.2 (±3.0)	-13.4 (± 3.0)
Global Circumferential Strain	-16.0 (±2.9)	-17.4 (± 4.8)	-16.9 (±5.1)
Global Radial Strain	27.9 (±1.4)	10.8(± 6.4)*	19.9 (± 17.6)

*p-value <0.05 control vs. pre-dialysis group (Mann Whitney test)

6.4. Left Ventricular Twist Characteristics:

At baseline, there was no difference in net twist and basal rotation between normal controls compared to renal patients prior to their dialysis session. However, there was a significant decrease in apical rotation between the control vs. pre-dialysis group (6.3^{o} ± 1.6 vs. 4.8^{o} ± 2.3, p = 0.01). **table 4.**

In contrast, there was no statistically significant difference in apical rotation **fig. 13**, basal rotation **fig. 14** and net twist **fig. 15** in renal patients before and after dialysis **Table 4.**

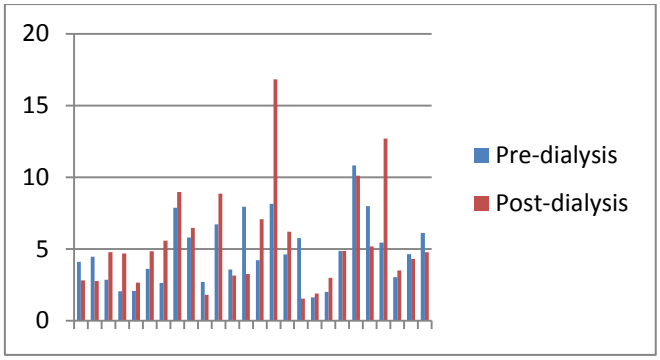


Figure 13. Apical rotation before and after dialysis. (Y-axis is in degrees, and X-axis are individual patients before and after dialysis)

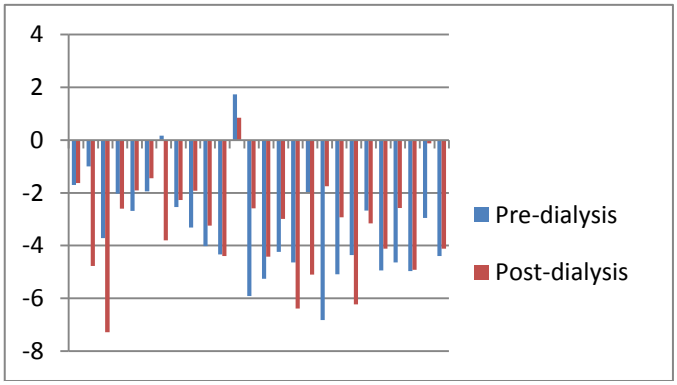


Figure 14. Basal rotation before and after dialysis (Y-axis is in degrees, and X-axis are individual patients before and after dialysis)

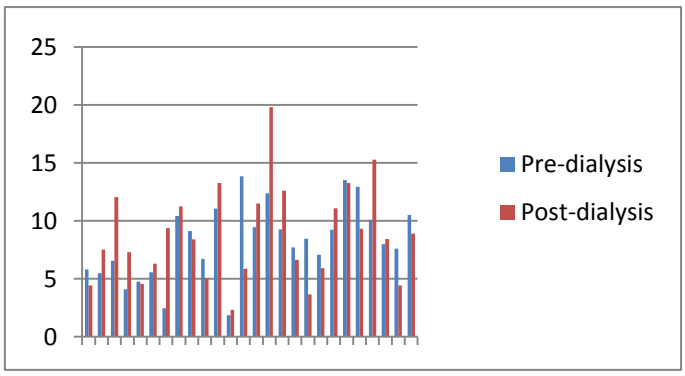


Figure 15. Net Twist before and after dialysis (Y-axis is in degrees, and X-axis are individual patients before and after dialysis

Table 4. Speckle Tracking twist characteristics

	Control (n=26)	**Pre-dialysis (n=26)**	**Post-dialysis (n=26)**
Apical Rotation (degrees)	6.3 (±1.6)	4.8 (±2.3)*	5.5 (± 3.6)
Basal Rotation (degrees)	-3.3 (±1)	-3.4 (± 1.9)	-3.3 (±1.9)
Net Twist	9.6 (±1.9)	8.2(± 3.1)	8.8 (± 4.1)

*p value <0.05 control vs. pre-dialysis group (Mann Whitney test)

6.5. Effects of anaemia on cardiac function and myocardial deformation.

The mean haemoglobin of the CKD patients was 9.9 ± 2.3 g/dl. The effect of this anaemia was analysed in relation to systolic function as measured by EF; diastolic function by examining E/E' ratios; apical rotation; basal rotation; net twist; GPLS; GPCS; and GPRS.

No statistically significant correlation was shown between haemoglobin levels and any of the following parameters: EF (r = 0.34, p = 0.38); apical rotation (r = 0.12, p=0.24); basal rotation (r = -0.17, p=0.63); net twist (r = 0.07, p=0.59); GPLS (r = - 0.02,p = 0.88); GPCS(r = 0.15, p = 0.42); and GPRS (r = -0.03, p = 0.61).

There was, however, a strong negative correlation between haemoglobin levels and diastolic dysfunction as measured by E/E' levels (r = -0.5; p <0.05). In other words increasing anaemia correlated with increasing incidence of diastolic dysfunction (or the lower the Hb, the higher the E/E' ratio and hence the greater diastolic dysfunction).

7.DISCUSSION

The chief finding of this study was that the components of myocardial deformation did not change significantly with the variable load and metabolic changes during haemodialysis despite a significant change in ejection fraction.

Other important findings were that 1) apical rotation and possibly GPRS are diminished in patients with CKD compared to normal controls and may represent early indicators of myocardial pathology in CKD patients; 2) LVH (88%) and diastolic dysfunction (92%) were common findings in our cohort; and 3) ejection fraction in our CKD cohort was remarkably well preserved despite a mean dialysis period of 6.7 ± 3.4 years.

7.1. Myocardial deformation as a measure of cardiac function.

The variable load and metabolic changes in CKD patients on dialysis make the accurate determination of left ventricular function challenging (6, 24). An increased pre-load prior to dialysis may lead to an overestimation of true systolic function as measured by EF as a result of Starling's Law, and decreased volumes post-dialysis resulting in a low EF(57). Afterload changes and changes in metabolites (which are negatively inotropic) would also have to be taken into account in an attempt to determine systolic function correctly.

In this study, it would be expected that cardiac volumes in CKD would be greater than in normal controls, and these volumes would decrease in renal patients after dialysis. For the most part, LVEDV, LAVI and LVESD do reflect this. It is surprising that other

dimensions such as LVESV, LVEDD and LVESD did not achieve significant differences, but observed trends were in keeping with expected changes, suggesting that the small numbers in this pilot study may account for this.

Ejection fraction would have been predicted to decrease post dialysis if the Starling effect were the only factor in play. Afterload did not make a significant contribution to EF since the surrogates of afterload, mean arterial pressure (MAP) and pulse pressure over stroke volume (pp/sv), did not change in renal patients before and after dialysis. Since EF did in fact increase after dialysis, one might conclude that the removal of toxic metabolites had an improved inotropic effect on the myocardium.

Why then did the components of myocardial deformation not change significantly? The available literature on the various components of myocardial deformation in CKD was reviewed in attempting to answer this question.

This is not the first study to examine strain in CKD patients on dialysis (58, 59). A study by Mendes et al.(59), examining the use of Tissue Doppler imaging (TDI) measuring longitudinal strain, failed to show any change in either EF or global longitudinal strain (as measured in an apical 4 chamber view (AP4C)) after dialysis. Mendes' conclusion was that the TDI measured longitudinal strain may be a relatively load independent measure of systolic function in the CKD patient. A study by Choi et al., used STE to measure longitudinal strain(58) also showed that global longitudinal strain did appear to change significantly when a 16 segment analysis of GLS was calculated but in the AP4C view alone (using only 6 segments) the change was less marked. When looking at longitudinal strain in segments (apex, mid and base), the mid-segment appeared to be sensitive to load; the

authors concluded that this may have been as result of a change in muscle fibre orientation with altered shape of the ventricle during dialysis. It is likely these segmental changes account for the difference between these two studies. In our study, we chose to use a six segment, AP4C calculation for GPLS. Therefore, it is not surprising that the GPLS did not change significantly in our study.

Global longitudinal strain to date is the most validated component of STE myocardial deformation(67). Studies have suggested a good correlation with systolic function (102, 103); hence, this study has chosen to use global longitudinal strain rather than segmental strain. GPLS appears to be a useful marker for systolic function in CKD and may be less sensitive to load changes compared to EF.

The effect of dialysis per se on circumferential and radial strain has not been extensively examined. A single cross sectional study has looked at circumferential, radial and longitudinal strain in CKD patients whether on haemodialysis or not(87). In this cohort of CKD patients, where EF was well preserved in all groups, longitudinal strain was diminished, but circumferential and radial strain was well preserved. Therefore, it may not be surprising that GPCS was not affected before and after dialysis in our study which may not have been adequately powered to show a difference in GPLS in CKD patients at baseline and following haemodialysis.

The results of radial strain in this study should be interpreted with caution. Out of a total of 312 segments that could be tracked in the 26 renal patients before and after dialysis,

28% of segments could not be tracked by the STE software. In addition, the standard deviation in the radial strain group was high. (See **fig 16. In the appendices)**

Left ventricular twist has not been examined in the CKD patients previously; our study is the first to do so. It represents the 'wringing' action of the heart and may represent a more efficient way in which the heart maximises systolic function; – 15% change in myocardial fibre length results in a 60% change in volume(104). Twist did not significantly change with dialysis in this study.

It appears from the available literature that certain components of myocardial deformation especially GPLS may be relatively load dependent (59). In this study, strain parameters did not change despite an increase in EF; this may imply that myocardial deformation is also less affected by uraemic metabolites. Whether this implies that myocardial deformation is a more robust measure of left ventricular function and contractility, giving us a measure of intrinsic myocardial function that is relatively independent of acute insults, which occur with the uraemic state, requires further studies.

7.2. Left Ventricular twist

Left ventricular twist requires further scrutiny. It is a composite action of the heart representing the difference in apical and basal rotation as a result of the orientation of fibres in the sub-epicardial and sub-endocardial layers. Apical rotation provides the

greatest contribution to twist; therefore, it may be an important finding that apical rotation is reduced in CKD patients at baseline despite a preserved EF.

The relative interplay between the right handed helical arrangement of the sub-endocardium, the left handed helical arrangement of the sub-epicardium, the pericardium and the global anatomy of the heart is key to understanding the observed changes in cardiac twist(66, 75, 91).

In normal cardiac physiology, apical rotation provides the greater contribution to net twist because of the larger radius of rotation of its sub-epicardial predominant fibres compared to the sub-endocardial predominant base.

For example, conditions that are known to affect mainly the sub-endocardial layer of the myocardium such as hypertensive left ventricular hypertrophy(105), aortic stenosis(77), hypertrophic cardiomyopathy(77), amyloidosis(106) and early myocardial ischaemia(107, 108) have been shown to cause apical hyper-rotation through the relatively unopposed sub-epicardial muscle fibres. Net twist is often normal or exaggerated with longitudinal strain being involved to a greater extent in some cases.

In comparison, disorders that have a transmural effect on the heart such as dilated cardiomyopathy and progressive ischaemic heart disease(109) cause a global decrease in twist.

The pericardium appears essential for cardiac twist(110) with animal studies showing a decrease in global twist with a pericardiotomy which improves once the pericardium is closed. Constrictive pericarditis with tethering of sup-epicardial myocardium results in diminished twist mechanics.

Using this model of understanding, it might be concluded that the isolated decrease in apical rotation in renal failure patients may represent the relative involvement of the sub-epicardial layer of the heart. It is unlikely that this represents significant transmural or pericardial disease since global rotation (and systolic function measured by ejection fraction) remained well preserved.

A 'layered' analysis of the effects of pathology of the epicardium relative to the endocardium of the myocardium may provide clues to the progression of the fibrosis seen in conditions such uraemic cardiomyopathy(34, 111, 112).

One might have expected an increase in apical rotation in our chronic kidney disease patients with the high incidence of hypertension (81%) and left ventricular hypertrophy in this cohort (113):Studies investigating cardiac twist in hypertensive patients with left ventricular hypertrophy and preserved systolic function are seen to have increased twist resulting from apical hyper-rotation(114). The implication of this study is that despite the degree of LV hypertrophy of this patient population, uraemic cardiomyopathy appears to impact the sub-epicardium more.

Further, with apical rotation the major contributor to net twist, one might expect a significant reduction in twist with the reduction apical rotation. The lack of effect seen on net twist may be from a compensatory increase in basal twist which follows the opposite pattern to apical twist with a relative increase compared to baseline rotation and a decrease after dialysis.

7.3. An integrated approach to interpreting myocardial deformation

It is likely that a complete understanding of myocardial deformation would require an appreciation of the complex relationships between the individual components of strain. As increasing data becomes available, there is a move to integrate our understanding of the relationships between types of strain in common conditions. In an article by Sengupta et. al.(115), the authors have attempted to show how such an approach adds to our understanding and diagnosis of heart failure syndromes**. (See fig 17 in the appendices)**

For example, the commonly observed pattern in non-renal hypertensive patients with left ventricular hypertrophy is that there is a reduction in GPLS which is associated with hyper-rotation of the apex and increase in twist (67, 113). Counter intuitively, in this study, significant LVH in CKD patients resulted in a reduction in apical rotation with relatively preserved longitudinal strain.

Understanding where in the myocardium the primary insult for any given condition impacts, may determine how the various components of strain may compensate. As

more studies emerge evaluating all four components of myocardial deformation in a variety of cardiac diseases, we may be able to determine how changes in strain correspond to known histopathological patterns.

7.4. Left ventricular hypertrophy, diastolic dysfunction, and Ejection Fraction in black patients with CKD

There are few studies looking at cardiac function in a Black South African CKD population. Hence, it may be important to note that the cardiac characteristics did not differ significantly from available international literature with the most common findings in our study being: concentric left ventricular hypertrophy and diastolic dysfunction.(3) This reflects the high incidence of hypertension as a reason for CKD requiring dialysis in our study group. The E/Ea ratio was particularly high in this CKD group 15.23 ± 5.22 as well as LVMI 156.1 ± 69.1 g/m^2. Both an E/Ea >15 and a LVMI >132 g/m^2 (in males) are independently associated with an increase in mortality (9, 116, 117).

It would be important to note in this South African group of CKD patients whether LVH is greater than in their western counterparts and whether it has similarly poor prognosis. In the retrospective study conducted by Luyckx et. al. at this institution, LVH was found in 72% of the 202 patient cohort. The high incidence of LVH in this group is not surprising with the high incidence of hypertension as a cause of ESRD in this population. However, this study probably drew the incorrect conclusion that because LVH was not associated with systolic dysfunction, it implied a better prognosis. Left ventricular hypertrophy does not necessitate a progression to systolic dysfunction(118). Moreover, hypertrophy is

thought to be associated with an increased risk of arrhythmias and sudden cardiac death(2) which would be difficult to confirm in a retrospective analysis.

This pilot study was not designed to answer these questions. Larger multicentre longitudinal studies will be required to achieve this end.

8.CONCLUSION

Speckle tracking echocardiography may still be in its infancy, but it has already enhanced our understanding of a wide variety of conditions. In this pilot study, STE strain imaging has been demonstrated to be a measure of cardiac function that may be less sensitive to load changes compared to EF with no significant difference seen in the four chief components of strain, despite significant volume changes during dialysis. In addition, reduced apical rotation in renal patients with a preserved ejection fraction, suggests that myocardial deformation analysis may offer us insights into early myocardial pathology before the advent of obvious systolic dysfunction. Larger, confirmatory validation studies would be needed to determine whether these were chance findings.

Though myocardial deformation holds early promise as a more sensitive measure of myocardial function in the CKD patient, there may be a complex interplay of the various components that make simplistic interpretation of any one measure insufficient.

9. LIMITATIONS AND FUTURE DIRECTIONS

This was a pilot study to examine the utility of myocardial deformation on dialysis. It was not adequately powered to provide definitive answers.

Larger validation studies with longitudinal follow up would be required to determine: 1) whether myocardial deformation is truly a relatively load independent of measure of ventricular function; 2) is apical rotation truly an early marker of cardiac pathology; 3) will segmental strain analysis reveal important further information about regional myocardium in CKD; and 4) whether the four components of myocardial deformation should be interpreted together as evaluation of individual types of strain may prove too simplistic.

Though we have tried to account for load changes, it will be far more of a challenge to dissect out the variable metabolic changes during dialysis. It would require the determination of electrolyte, acid-base, calcium and phosphate levels before and after dialysis. This study was designed to be a pilot study, to determine the feasibility of future studies with minimal discomfort to patients.

Speckle tracking echocardiography is a novel technique with left ventricular twist the most recent component of strain studied. Though echocardiographic equipment has new levels of sophistication and improves daily, there are technical demands on the physician and sonographer in both the acquisition of measurements and the off-line measurement

of images. Image acquisition is the most important requirement to optimise speckle tracking analysis. Positioning of the transducer, expiratory and inspiratory views are all essential elements to STE. The author's personal experience was that there is a steep learning curve in learning the techniques for STE. Currently, STE may not yet be ready for use by the inexperienced cardiologist or sonographer outside of a core echocardiography laboratory as is available at this institution.

Because we are at the infancy of this technology, there is not yet standardisation between the vendors of echocardiographic equipment. Each company has developed their own hardware and software algorithms that process the raw imaging data differently. 'Normal' values acquired for any given vendor cannot be considered universal. For this reason, this cardiac unit has for this study and part of an on-going effort been establishing data for our local population(90). These problems have been acknowledged by echocardiologists across the world(68), and there are moves to encourage vendors to standardise program algorithms.

Further, the paucity of data on the cardiac function in CKD patients in South Africa requires large multicentre studies to determine the natural history in our populations and determine the most appropriate medical management.

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APPENDICES

APPENDIX 1

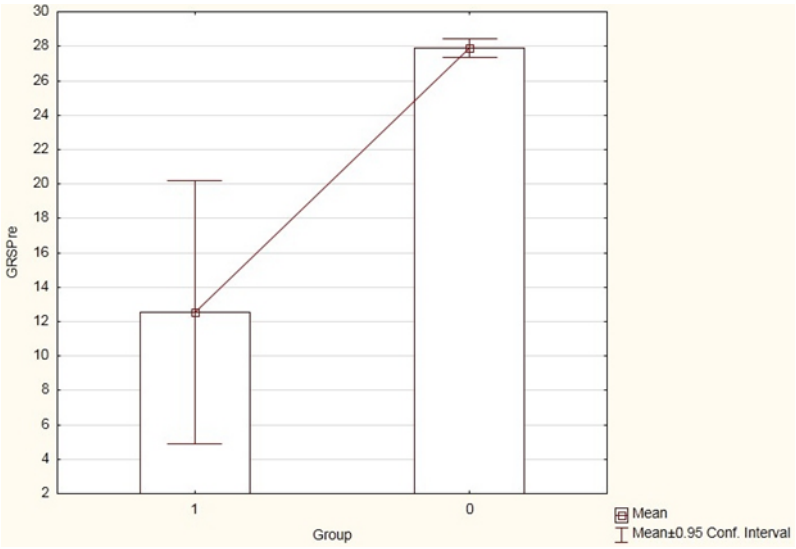


Figure16. Mean plots of Global Peak Radial Strain (GPRS) in group 1 (Renal patients before dialysis) and group 0 (Control group). Though the p value for these means suggest significance (p= <0.01), note that there is a wider range of values in the 95% confidence interval for renal patients compared to the tighter range in the control group.

APPENDIX 2.

Classification of cardiac mechanics in heart failure

Functional impairment	Longitudinal mechanics	Circum-ferential mechanics	Torsional mechanics	Global EF	Diastolic filling pressures	Clinical syndrome
Subendocardial dysfunction	Impaired	Preserved	Preserved	Preserved	Elevated	Diastolic HF
Subepicardial dysfunction	Preserved	Impaired	Impaired	Preserved	Elevated	Diastolic HF
Transmural dysfunction	Impaired	Impaired	Impaired	Impaired	Elevated	Systolic HF

Abbreviations: **EF:** ejection fraction **HF**: heart failure

Fig. 17. Cardiac Mechanics of heart failure

APPENDIX 3.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Anthony Yip

CLEARANCE CERTIFICATE	**M10510**
PROJECT	The Effect of Load Changes on Myocardial Deformation and Velocity as Measured by Speckled Tracking Echocardiography in Black Patients on Dialysis
INVESTIGATORS	Dr Anthony Yip.
DEPARTMENT	Department of Cardiology
DATE CONSIDERED	28/05/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/06/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof MR Essop

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

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APPENDIX 4

1. Patient information sheet:

A. For chronic kidney disease patients on haemodialysis

A study to look at heart function on patients on dialysis:

Good morning, I am Dr Anthony Yip, a consultant in the Cardiology Department at Chris Hani Baragwanath Hospital. I wish to invite you to participate in a study that is being conducted by the Cardiology and Renal departments at Chris Hani Baragwanath Hospital and the University of the Witwatersrand.

There is evidence that the heart is the most common organ to be affected by kidney disease, and the aim of our study is to look at improved ways to look at the heart accurately. There is especially a lack of information on the use of newer ultrasound techniques in patients of African origin.

The study will be studying heart function in patients on chronic dialysis using an ultrasound examination of the heart.

We are looking for 20 male and 20 female volunteers, between 20 to 60 years of age, of African origin on dialysis at the Chris Hani Baragwanath Hospital.

This study is non-invasive – there will be no extra blood test beyond what your own kidney doctors are taking for your treatment.

We will be obtaining information about your medical history, and get blood results recorded in your files.

On the day of your routine dialysis session, we would like to perform an ultrasound examination on you just before your dialysis session, and immediately after your session.

The ultrasound examination involves a trained technologist or doctor using gel and plastic ultrasound probe on the surface of your chest to look at your heart. We will take your blood pressure before each ultrasound.

The entire examination should take about 30 to 40 minutes.

All information obtained will be held with the strictest confidence. Your name and your information will not be provided to any third party. You can withdraw consent to be part of this study at any time and your treatment will not be affected in any manner.

Thank you for your time and consideration.

Dr Anthony Yip

Please contact Dr Anthony Yip on the following telephone numbers for any queries on this study:

(011) 933-8197 (w)

(011)938-8945 (fax)

082-825-6340 (mobile phone)

Or e-mail on dranthonyyip@gmail.com

Should there be any complaints or concerns you may have on any aspect of this study, please contact Professor Cleaton-Jones or Ms Anisa Keshav from the Ethics Committee of the University of the Witwatersrand on:

(011) 717-1234

(011) 717-1265(fax)

Or e-mail Ms Keshav on anisa.keshav@wits.ac.za

B. Information sheet for health volunteers.

Good morning, I am Dr Anthony Yip, a consultant in the Cardiology Department at Chris Hani Baragwanath Hospital. I wish to invite you to participate in a study that is being conducted by the Cardiology and Renal departments at Chris Hani Baragwanath Hospital and the University of the Witwatersrand.

We are examining the use of a new ultrasound technique to examine the heart.

We are looking for healthy volunteers of African origin: 20 male and 20 female subjects between 20 and 60 years of age to act as a control group for our study.

The ultrasound examination involves a trained technologist or doctor using gel and plastic ultrasound probe on the surface of your chest to look at your heart. We will take your blood pressure before each ultrasound.

The entire examination should take about 30 to 40 minutes.

All information obtained will be held with the strictest confidence. Your name and your information will not be provided to any third party.

You can withdraw consent to be part of this study at any time.

Thank you for your time and consideration.

Dr Anthony Yip

Please contact Dr Anthony Yip on the following telephone numbers for any queries on this study:

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Should there be any complaints or concerns you may have on any aspect of this study, please contact Professor Cleaton-Jones or Ms Anisa Keshav from the Ethics Committee of the University of the Witwatersrand on:

(011)717-1234

(011) 717-1265(fax)

Or e-mail Ms Keshav on anisa.keshav@wits.ac.za

2. Patient consent form:

Please read through our patient information carefully.

If there is any aspect of our study that you do not understand, please ask the doctor explaining the study to you.

Please do not sign this form until you are sure what this study means to you.

Your consent to be part of this study only entitles anyone involved in this study to use the information for academic purposes and to improve health care for our patients.

You may withdraw your consent at any time without fear of consequences.

I Mr/Mrs/Ms/Miss/Dr _____give Dr Anthony Yip, the Departments of Cardiology and Nephrology at Chris Hani Baragwanath Hospital, and the University of the Witwatersrand, consent to collect my clinical history, clinical information and perform clinical and ultrasound examinations as explained to me for the express purposes of clinical research. My patient and confidentially rights will be retained. I acknowledge in signing this form, I have read and fully understand the patient information and this consent form.

Signed: _____ **Witness: _____**

Date: _____ **Date: _____**

APPENDIX 5

PATIENT DATA SHEET

Patient Name			**Hospital Number:**	
Contact Details				
	Address			
	Telephone	**Work**		
		Home		
AGE				
GENDER	**MALE**		**FEMALE**	
Vital Data				
	Identity number		**Date of Birth**	
	Height			
	Weight	**Before Dialysis**		
		After Dialysis		
	Blood Pressure	**Before Dialysis**		
		After Dialysis		

Baseline blood results		Date	Value	
	Haemoglobin			
	Albumin			
	Parathyroid Hormone			
	Calcium			
	Phosphate			

Transthoracic ECHO value	Date	Pre dialysis/ Baseline value in Control subjects	Post dialysis	
LVEDD				
LVESD				
LVEDV				
LVESV				
LA				
LAVI				
Ejection Fraction (Fractional Shortening)				
Ejection fraction (Modified Simpsons)				
Fractional				

Shortening				
IVSD				
LV Mass				

Speckle tracking Strain measurements

Segment:		Patient Values		Normal Reference
Longitudinal		Pre Dialysis	Post Dialysis	Strain(%) and SD
	Apicolateral			21%(7)
	Apicoseptal			23%(6)
	Mid Lateral			19%(6)
	Mid Septal			19%(4)
	Basolateral			19%(6)
	Basoseptal			17%(4)
Circumferential				
Mid				
	Anterior			
	Anteroseptal			
	Septal			
	Lateral			
	Posterior			
	Inferior			
Radial				
Mid				
	Anterior			

	Anteroseptal			
	Septal			
	Lateral			
	Posterior			
	Inferior			

APPENDIX 6

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)

Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

28 January 2013

Dr Anthony Yip
Division of Cardiology
Chris Hani Baragwanath
Academic Hospital
University

Sent by e-mail to: dranthonyyip@gmail.com

Dear Dr Yip

RE: **Protocol M10105: 'The Effect of Load Changes on Myocardial Deformation and Velocity as Measured by Speckle Tracking Echocardiography in Black Patients on Dialysis**
Protocol amendment

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (medical) has reviewed and approved your request to 'extend the age range from 20-60 to 20-65 years of age' on the abovementioned protocol as detailed in your letter dated 30 December 2012.

Thank you for keeping us informed and updated.

Yours sincerely,

Anisa Keshav
Administrator
Human Research Ethics Committee (Medical)