PREVALENCE OF PULMONARY HYPERTENSION IN ADULT PATIENTS WITH CHRONIC KIDNEY DISEASE AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

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A Research Thesis submitted in partial fulfillment of the requirements for the award of the degree of Masters of Medicine in Internal Medicine, Moi University

DECLARATION

Declaration by Candidate

This thesis is my original work and has not been presented for a degree or any academic credit in any other university or examining body. No part of this proposal may be reproduced without the prior written permission of the author or Moi University.

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DEDICATION

I dedicate this thesis to my family for the support they granted me to realize this achievement and to all my teachers for their invaluable guidance.

ABSTRACT

Background: Pulmonary hypertension is defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiographywhile Chronic Kidney Disease (CKD) isthe presence of kidney damage or decreased kidney function for three or more months, with eGFR<60mls/min irrespective of the cause. The prevalence of pulmonary hypertension (PHTN) is much higher among patients on hemodialysis in studies done in Non-African population and has been associated with a worse outcome. However, theextent of PHTN has not been established in Kenyan patients withCKD on and without hemodialysis.

Objective: To determine the prevalence of pulmonary hypertension among CKD patients with and without dialysis and to compare their clinical, hemodynamic and metabolic variablesat the Moi Teaching and Referral Hospital (MTRH).

Methods: This cross-sectional hospital based study was conducted among adult patients with Chronic Kidney Disease with or without dialysis in the renal and adult medical wards in MTRH, Eldoret, Kenya.Pulmonary hypertension was defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography and CKD as the presence of kidney damage or decreased kidney function for three or more months with eGFR<60mls/min irrespective of the cause.All patients who met the inclusion criteria were enrolled by prospective consecutive sampling. Demography(age, gender), clinical (history and physical examination), transthoracic Doppler echocardiography and laboratory (hemoglobin,hematocrit, BUN, creatinine, potassium, phosphate and calcium levels, albumin, AST and ALT levels, HIV test and RBS) were done. Data were collected using a structured interviewer administered questionnaire, keyed into Microsoft Excel® database and analyzed using STATA version 13®. Descriptive statistics were summarized in tables and graphs and correlations were done using Pearson's Chi Square test.

Results: Among the 132 participants included in the final analysis, 82(62%) were male, median age 47 years (IQR 31-59).Only 8% and 2% of the participants reported current history of alcohol use and smoking respectively.Majority (82%) of the participants were hypertensive with a median blood pressure of 150/90 mmHg (IQR 131/75-168/100). An estimated 81% of the participants were on antihypertensives. An estimated 28% of the participants were diabetic, with approximately 15% and 11 % of them being on oral hypoglycemics and insulin respectively. Majority of the participants (78%) were on dialysis, with most (71%) having only one session of dialysis per week. The most common venous access site was subclavian/internal jugular catheter (87%), compared with arteriovenous fistula (11%) and tunneled catheter (2%) respectively.Overall 70/132 participants (53%) had pulmonary hypertension. The prevalence of pulmonary hypertension was higher among participants on dialysis 63/100 (63%) compared to those not on dialysis 7/32 (22%). Patients on dialysis had higher odds of having pulmonary hypertension (OR 5.9; 95%CI 2.4-15.2; p 0.0001) compared with patients not on dialysis.All other factors assessed (such as gender, age, weight, hemoglobin, hematocrit, calcium and potassium) were not significantly associated with pulmonary hypertension.

Conclusion: The prevalence of pulmonary hypertension in CKD patients is high at MTRH and it is higher in those on dialysis compared to those not on dialysis.

Recommendations: Due to the high prevalence of PHTN in CKD patients, routine screening is recommended for early detection and management. Large prospective studies using right heart catheterization are needed to establish the true prevalence of pulmonary hypertension in CKD.

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KEY WORDS AND ABBREVIATIONS

ADMA- Asymetricdimethylarginine

ALT- Alanine Aminotransaminase

AST- Aspartate Aminotransaminase

AVF - Arteriovenous Fistula

BUN- Blood Urea Nitrogen

CKD- Chronic Kidney disease

ESRD- End Stage Renal Disease

eGFR – Estimated Glomerular Filtration Rate

FGF- Fibroblast Growth Factor

HD- Hemodialysis

HIV- Human Immunodeficiency Virus

IREC - Institutional Research and Ethics Committee

MTRH- Moi Teaching & Referral Hospital

NO- Nitric Oxide

NOS- Nitric Oxide Synthase

NYHA- New York Heart Association

PAP- Pulmonary Arterial Pressure

PD- Peritoneal Dialysis

PDGF- Platelet Derived Growth Factor

PHTN/PH - Pulmonary Hypertension

RBS- Random Blood Sugar

RVSP- Right Ventricular Systolic Pressure

SPAP - Systolic Pulmonary Arterial Pressure

TGF- Transforming Growth Factor

DEFINITION OF KEY WORDS

Pulmonary Hypertension- systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography.

Chronic kidney disease- the presence of kidney damage or decreased kidney function for three or more months,with eGFR<60mls/minirrespective of the cause.

CHAPTER ONE: INTRODUCTION

1.1 Background

Pulmonary hypertensionis defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography(Yigla et al., 2003) and is classified into five groups by the World Health Organization (Appendix XI). Pulmonary hypertension is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology(Emara et al., 2013). Its presence in CKD has been recently suggested to occur in considerable portions of patients and has been associated with a worse outcome.(Kosmadakis, Aguilera, Carceles, Da Costa Correia, & Boletis, 2013).Whether the pulmonary hypertension arises from cardiac, pulmonary, or intrinsic vascular disease, it generally is a feature of advanced disease. Because the causes of pulmonary hypertension are so diverse, it is essential that the etiology underlying the pulmonary hypertension be clearly determined before beginning treatment.

Pulmonary arterial hypertension (PAH) one form of pulmonary hypertension characterized by elevated pulmonary pressureis a newly recognized disease in patients with renal disease(Unal et al., 2010). A study by Havlucu et.al demonstrated a high prevalence of PHTN among patients with CKD(Havlucu et al., 2007).Bolignano et.al in their study showed that prevalence of PHTN ranges from 9%-39% in individuals with stage 5 CKD, 18.8- 68.8% in hemodialysis patients, and 0-42% in patients on peritoneal dialysis(Bolignano et al., 2013). There is no epidemiological data available yet for earlier stages of CKD(Bolignano et al., 2013).

In recent reviews done by Emara et.al in nephrology center of King Fahd hospital, Al-Madinah Al-Munawarah, the Kingdom of Saudi Arabia, the prevalence of pulmonary hypertension in

CKD was reported to be around 40-50%(Emara et al., 2013)with prevalence of PHTN ranging from 18.8 to 68.8% in hemodialysis patients(Bolignano et al., 2013).

Chronic hemodialysis patients are exposed to continuous pulmonary insults of multifactorial origin. High cardiac output (CO) resulting from the arteriovenous fistula (AVF)), fluid overload, anemia,metabolic,hormonal derangements,endothelial dysfunction and sleep-disordered breathingthat occurs in CKDas well as exposure to dialysis membranes may lead toincreased pulmonary arterial pressures and lead topulmonary hypertension (Okura H, 1994). Moreover, pulmonary calcification in chronic dialysis patients has been associated with pulmonary dysfunction(Milliner DS, 1990).

Correcting volume overload and treating left ventricular disorders are factors of paramount importance for relieving PHTN in patients in CKD

There is lack of epidemiological data on pulmonary hypertensionfor earlier stages of CKD(Bolignano et al., 2013).PHTN in patients with CKD may be induced or aggravated by left ventricular disorders and risk factors typical of CKD, including: volume overload, an AVF, severe anemia(Bolignano et al., 2013). PHTN is a common clinical condition among patients with ESRD evaluated for renal transplantation. The duration of time on renal replacement therapy particularly if HD is the treatment of choice is associated with greater prevalence of PHTN. Since it may be of prognostic importance in patients undergoing renal transplantation, a careful preoperative assessment including a comprehensive Doppler echocardiographic examination is needed to identify PHTN(Bozbas et al., 2009). Furthermore, PHTN has been associated with higher morbidity and mortality in CKD patients

1.2 Problem Statement

Pulmonary hypertension is a newly recognized disease in patients with renal disease which has previously been ignored and possibly contributes to morbidity and mortality.PHTN in patients on hemodialysis as well as peritoneal dialysis is a strong independent predictor of mortality, nearly equal to that associated with long-standing severe cardiac abnormalities. Mortality rates remain exceedingly high with 15%, 30%, and 45% mortality at 1, 2, and 3 years after diagnosis, respectively. Many etiologies causing PHTN have been reported, and one of the background diseases seen in patients with PHTN is chronic kidney disease.However, little has been done regarding determining the prevalence and the clinical correlates of pulmonary hypertension in this population of CKD in this North Rift part of Kenya so as to guide clinicians of higher index of suspicion and timely investigation to institute appropriate management.

1.3 Research question

1. What is the prevalence of pulmonary hypertension in adult patients with CKD inMTRH and what are the clinical characteristics seen in this population.

1.4 Broad objective

Evaluate the prevalence of pulmonary hypertension among CKD patients.

1.5 Specific objectives

1. To determine the prevalence of pulmonary hypertension in patients with CKD in MTRH.
2. To determinethe proportion of pulmonary hypertension in CKDpatients with dialysis compared to those without dialysis in MTRH.
3. To assess the clinical characteristics seen in patients with and without PHTN in CKD

1.6 Justification

Pulmonary hypertension (PHTN) has been reported to be high among end-stage renal disease (ESRD) patients(Kosmadakis et al., 2013)and contributes greatly to morbidity and mortality in this group of patients. Established PHTN is irreversible hence early detection and management is needed.

Research of the same has been done in Non- African population and limited ones have been done in Kenya especially the western region. Results of this study will go a long way in bridging the gap in terms of establishing the extent of PHTN in this region of Kenya and the associated clinical characteristics thus guiding clinicians on timely diagnosis and intervention.

Further research of this devastating disorder is warranted in this group of patients. More basic and further clinical research is needed in order to improve our knowledge on the pathogenetic factors as well as more sophisticated therapeutic options that may improve the morbidity, mortality, and quality of-life parameters in dialysis patients with PH.

CHAPTER TWO: LITERATURE REVIEW

2.1 Prevalence of PHTN in CKD

Pulmonary hypertension (PHTN) is a disease characterized by elevated pulmonary artery pressure, which often results in right ventricular failure. It may be idiopathic, familial, or associated with multiple other diseases. PHTN occurs in men and women of any race or age (Kosmadakis et.al, 2013).

The gold standard definition of pulmonary hypertension is an increase in mean pulmonary arterial pressure > 25mmHg at rest as assessed by right heart catheterization.Alternatively, pulmonary hypertension can be defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography(Yigla et al., 2003).

A meta-analysis carried out to predict pulmonary pressure using doppler echocardiography compared with right heart catheterization reported a sensitivity and specificity of 88% and 56% respectively(Taleb, Khuder, Tinkel, & Khouri, 2013). The prevalence of PHTN is estimated to be 40% in hemodialysis patients secondary to the type of vascular access (both central venous catheter and arteriovenous fistula)(Di Lullo et al., 2013).

PHTN has been recently suggested to be associated with a worse outcome in patients with CKD(Kosmadakis et al., 2013).

Mortality rates of PHTN in CKD remain exceedingly high with 15%, 30%, and 45% mortality at 1, 2, and 3 years after diagnosis, respectively(Humbert, 2010).

Pulmonary hypertension (PHTN) is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology (Kosmadakis et al., 2103).

Pulmonary hypertension (PHTN) is a newly recognized disease in patients with renal disease(Bolignano et al., 2013). There is a high prevalence of PHTN among patients with ESRD on chronic HD via a surgical A-V fistula(Nakhoul, Yigla, Gilman, Reisner, & Abassi, 2005).

In recent reviews by Emara et.al in Saudi Arabia, the prevalence of pulmonary hypertension in CKD was reported to be around 40-50%(Emara et al., 2013).

Bolignano et.al in their study showed that prevalence of PHTN ranges from 9%-39% in individuals with stage 5 CKD, 18.8- 68.8% in hemodialysis patients, and 0-42% in patients on peritoneal dialysis (Bolignano et al., 2013). There is no epidemiological data available yet for earlier stages of CKD(Bolignano et al., 2013).

A study by Soki et. al at Kenyatta National Hospital in Nairobi showed a prevalence of PH among CKD patients of 32.5%, with a median SPAP of 47.3mmHg and a range of 36.1–79 mmHg. A strong association between PH and ejection fraction of less than 50%, as a marker of LV dysfunction, was demonstrated (Soki et.al., 2017)

PHTN in patients with CKD may be induced or aggravated by left ventricular disorders and risk factors typical of CKD, including: volume overload, an AVF, sleep-disordered breathing, exposure to dialysis membranes, endothelial dysfunction, vascular calcification, severe anemia (Bolignano et al., 2013).

PHTN is a common clinical condition among patients with ESRD evaluated for renal transplantation. The time on renal replacement therapy particularly HD as the treatment is associated with greater prevalence.

Since it may be of prognostic importance in patients undergoing renal transplantation, a careful preoperative assessment including a comprehensive Doppler echocardiographic examination is needed to identify PHTN.

Correcting volume overload and treating left ventricular disorders are factors of paramount importance for relieving PHTN in patients with CKD (Bolignano et al., 2013).

2.2 Epidemiology

The estimated incidence of primary pulmonary hypertension is 1 to 2 cases per 1 million persons in the general population. During childhood, the condition affects both genders equally; after puberty, it is more common in women than in men (ratio: 1.7 to 1). Primary pulmonary hypertension is most prevalent in persons 20 to 40 years of age. The condition has no racial predilection (LJ., 1997).

Secondary pulmonary hypertension is relatively common but is underdiagnosed. Reliable estimates of the prevalence of this condition are difficult to obtain because of the diversity of identifiable causes (Yigla et al., 2009).

In a single center study from Israel by Fruchter and Yigla, hemodialysis was the third most common etiologic factor associated with the development of PHTN (13% of the total cases) after chronic respiratory disease (31%) and collagen vascular disease (Yigla et al., 2009).In persons more than 50 years of age, cor pulmonale, the consequence of untreated pulmonary hypertension,

is the third most common cardiac disorder (after coronary and hypertensive heart disease)(Palevsky HI, 1990).

PHTN in patients on hemodialysis as well as peritoneal dialysis is a strong independent predictor of mortality, nearly equal to that associated with long-standing severe cardiac abnormalities

In another interesting study by Yigla et al. from Israel in 2009, the risk of death in hemodialysis patients with PHTN is independent of the circumstances of the occurrence of this disorder, that is, the risk of mortality in patients with PHTN associated with arteriovenous access formation and initiation of hemodialysis therapy is not significantly different from those who suffered from PHTN due to cardiac disorders before dialysis initiation (Yigla et al., 2009).

2.3 Pathogenesis

There are several factors that play a role in the pathogenesis of PHTN, including genetic predisposition and exposure to toxins and/or inflammatory mediators(Martin, Klinger, & Rounds, 2006). These inciting factors lead to multiple abnormalities, including endothelial cell proliferation and dysfunction, thrombotic obliteration of vascular lumen, abnormal vasomotor control and chronic remodeling of the vascular wall(Martin et al., 2006).

According to the recent WHO classification from 2008 pulmonary hypertension can be categorized as pulmonary arterial hypertension, pulmonary venous hypertension, hypoxic pulmonary hypertension, chronic thromboembolic pulmonary hypertension and pulmonary hypertension from other causes (Dana Point 2008).

Because of the range of medical conditions and environmental exposures associated with pulmonary arterial hypertension, it is difficult to envision a unifying pathogenic mechanism.

Although there are probably genetic determinants, environmental exposures and acquired disorders that predispose the patients to pulmonary arterial hypertension, it is clear that none of the factors alone are sufficient to activate the pathways essential for the development of this vascular disease(Kolilekas L, 2006; Soroush-Yari A, 2005).

Local vascular tone and function are regulated by the balance between vasodilators, such as prostacyclin and nitric oxide, and vasoconstrictors, such as thromboxane A2 and endothelin-1 (Jeffery TK, 2002; Perez-Penate G, 2005).Increase in endothelin-1, a powerful pulmonary vasoconstrictor, has been shown in patients with CKD (DP:, 1996). Impaired nitric oxide production and reduced sensitivity to nitric oxide have been described in patients with CKD(ND et al:, 2001).With the vasodilatory and antimitogenic properties of NO, it is possible that the attenuated basal and HD-induced NO production in patients with PHTN contributes to the increased pulmonary vascular tone (Nakhoul et al., 2005).Endothelial dysfunction, together with lower activation of NOS, increased levels of serum endothelin and fibrin storages, involves an extensive growth of endothelial cells leading to complete obliteration of pulmonary vessels(Di Lullo et al., 2013).

Altered ET-1 levels may be involved in the pathogenesis of rebound hypertension and hypotension during HD (El-Shafey, El-Nagar, Selim, El-Sorogy, & Sabry, 2008).

Pulmonary arterial hypertension is characterized histopathologically by vasoconstriction, vascular proliferation, in situ thrombosis, and remodeling of all 3 levels of the vascular walls.

PHTN involves vasoconstriction and obliteration of the lumen of small vessels in the lungs by plexiform lesions resulting in increased resistance to flow. Proposed mechanisms for the

formation of the plexiform lesion include dysregulation of endothelial growth and angiogenic response to local triggers (Jeffery TK, 2002).

The partial restoration of normal PAP and CO in HD patients undergoing either temporal A-V shunt closure or successful transplantation indicates that excessive pulmonary blood flow is involved in the pathogenesis of the disease (Nakhoul et al., 2005). Secondary pulmonary hypertension in chronic kidney disease patients is strictly related to pulmonary circulation impairment together with chronic volume overload and increased levels of cytokines and growth factors, such as FGF(fibroblast growth factor), PDGF(platelet derived growth factor), and TGF-β(transforming growth factor) leading to fibrosis (Di Lullo et al., 2013; Wedgwood et al., 2007).

Extraosseous pulmonary calcification is found most commonly in patients with CKD receiving hemodialysis (Bendayan D, 2000; Chan ED, 2002; DNS Kerr, 1997). Calcification can occur in any tissue of the body but is found most commonly in the heart, lungs, kidney and stomach. In the lungs, calcium deposits have been found in the interstitium of the alveolar septum, bronchial walls and even in the walls of the pulmonary vessels. Autopsy studies of hemodialysis patients carried out by Conger et. al have shown that pulmonary vascular calcification occurs frequently(Conger JD, 1975; Kuzela DC, 1977; Yigla et al., 2003). In its mild form, fine linear and granular deposits along the alveolar capillary wall were noted, while the severe forms had linear calcification of the elastic laminae and muscle fibers that in some cases were accompanied by loose intimal fibrosis with narrowing of the vessel lumens .Affected vessels become stiffer independent of age or hypertension. In contrast to Conger's et.al findings ,Amin et.al study did not demonstrate the relation between pulmonary artery calcification and PHTN(Amin M, 2003;). In the study carried out by Havlucu and his team showed higher serum parathyroid

hormone levels and calcium-phosphate product, independent of the effects of hemodialysis and AVF, in patients with PHTN in comparison with patients without PHTN(Havlucu et al., 2007).

These pathologic changes result in progressive increases in the mean pulmonary artery pressure and pulmonary vascular resistance, which, if untreated leads to right-ventricular failure and death.

Early in the disease process, the signs and symptoms of PHTN are often nonspecific, making diagnosis challenging.Patients often present with progressively worsening dyspnea and fatigue and those with severe pulmonary arterial hypertension die of right heart failure.

2.4 Risk factors and Pathophysiology

2.4.1 LV Disorders, Volume Overload, and Lung Disease

Hypertension and diabetes mellitus are 2 dominant causes of kidney disease. They trigger LV diastolic dysfunction, an alteration bound to increase pulmonary venous and arterial pressure(Tiengo, Fadini, & Avogaro, 2008).

Chronic volume overload, a factor implicated in LV disorders and in the high venous return in patients with CKD, may induce pulmonary venous hypertension by both increasing pulmonary blood flow and adversely affecting LV function.

In addition, myocardial stiffness secondary to myocardial infarction, another frequent complication of CKD, may contribute to pulmonary hypertension. In categorical terms, patients with LV disorders and/or volume overload constitute group II of the WHO classification, whereas patients with lung diseases, either restrictive (obese patients with CKD) or obstructive

(patients with chronic obstructive pulmonary disease), are grouped in WHO class III(Badesch et al., 2009).

In chronic obstructive pulmonary disease, the main mechanism underlying increased pulmonary pressure is chronic hypoxia, a potent pulmonary vasoconstrictor(AM, 2011). If sustained, vasoconstriction in the lung leads to extensive remodeling of the pulmonary vessels and a steady reduction in vessel compliance, a phenomenon which in and of itself contributes to pulmonary hypertension(Sakao S, 2010).

Pulmonary capillary wedge pressure is considered to be a reliable marker for LV end-diastolic pressure. However, determining whether left-sided cardiac disease is present on the basis of pulmonary capillary wedge pressure is unreliable in patients with pulmonary hypertension because ~50% of patients who are considered to have pulmonary artery hypertension on the basis of pulmonary capillary wedge pressure eventually may turn out to have WHO class II pulmonary hypertension instead when diagnosed on the basis of LV end-diastolic pressure (Halpern SC, 2009). Thus, when there is a choice between pulmonary capillary wedge pressure and LV end-diastolic pressure in a patient with pulmonary hypertension, LV end-diastolic pressure should be regarded as the gold standard for the diagnostic definition of pulmonary hypertension.

2.4.2 Arteriovenous Fistula

An AVF leads to decreased systemic vascular resistances, enhanced venous return, and increased cardiac output to maintain proper blood flow to all organs and tissues. These adaptations increase pulmonary blood flow and set the stage for pulmonary hypertension. Because pressure is the product of flow and resistance, increased pulmonary flow necessarily leads to increased pressure at any level of pulmonary vascular resistance. Well-performed studies

show that pulmonary pressure increases in strict temporal relationship with AVF creation(Abassi Z, 2006) and that pulmonary hypertension tends to worsen over time in this population(Fabbian F, 2010; Havlucu et al., 2007).

2.4.3 Exposure to Dialysis Membranes

Neutrophil activation secondary to blood–dialysis membrane contact accompanied by reversible neutrophil sequestration in the lung, a phenomenon that was intensively investigated in the 1980s,(F. J. Craddock PR, Brigham KL, Kronenberg RS, Jacob HS., 1977; F. J. Craddock PR, Dalmasso AP, Brigham KL, Jacob HSJ 1977) contributes to causing or worsening microvascular lung disease in HD patients(Yigla M, 2006).

This phenomenon is particularly pronounced when dialysis is performed using cellulosic membranes and is attenuated but not abolished with synthetic and modified cellulosic membranes. In a crossover trial of a series of 74 patients without an AVF who were dialyzed through a central venous catheter, use of high-flux polysulfone filters was associated with a more pronounced decrease in post dialysis pulmonary pressure than the use of cellulose acetate filters(Kiykim AA, 2010).The hypothesis that volume overload and LV disorders triggered or exacerbated by kidney disease and repeated exposure to dialysis membranes may cause pulmonary hypertension independently of the AVF and other factors is supported by the demonstration that kidney transplantation may revert pulmonary artery pressure to normal in patients who still have a functioning AVF (Nakhoul et al., 2005).

2.4.4 Systemic Diseases Associated With CKD

Pre-existing connective tissue diseases(Gurubhagavatula I, 1997) and superimposed infectious(Mesa RA, 1998), hematologic, and liver diseases can all contribute to pulmonary hypertension in patients with CKD by mechanisms that interfere with the control of microvascular tone in the lung . However, collectively, these factors largely fail to explain the high prevalence of pulmonary hypertension in dialysis patients because most patients with CKD exhibit pulmonary hypertension even in the absence of these diseases(Yigla M, 2006).

2.4.5 Sleep-disordered Breathing

Sleep apnea is a factor of paramount importance for the high risk of pulmonary hypertension in the setting of CKD. Episodes of nocturnal hypoxia, the key pathophysiologic effect of sleep apnea, are frequent in patients with CKD regardless of whether they are dialysis dependent(Sakaguchi Y, 2011; Zoccali C, 2002). Volume overload is a major factor in sleep apnea, particularly in patients with kidney disease. Nocturnal hypoxemia arising from sleep apnea is a strong trigger of pulmonary hypertension in experimental models,(Ressl J, 1974) and a close link between oxygen saturation and pulmonary artery pressure has been established in clinical physiology experiments in both healthy persons and patients with chronic obstructive pulmonary disease (Ward JP, 2009). Sympathetic activation is the main mechanism whereby hypoxemia increases pulmonary pressure (Sica AL, 2000). In this respect, it is interesting to note that patients with sleep-disordered breathing have increasedasymetricdimethylarginine(ADMA) levels (Barceló A, 2009). Furthermore, circulating levels of this NO synthase inhibitor are associated with sympathetic nerve activity (as assessed by measurements in the peroneal nerve) in patients with CKD(Grassi G, 2011) and with norepinephrine levels in dialysis

patients(Mallamaci F, 2004). Given the strong vasoconstriction potential of ADMA in the lung vasculature and the observation that sympathetic nervous system activity and ADMA seem to share a common pathogenic pathway that is conducive to LV hypertrophy(Grassi G, 2011) in patients with CKD and to cardiovascular events in dialysis patients,(Tripepi G, 2011) it appears possible that the same pathogenic pathway be implicated in pulmonary hypertension in these patients.

2.4.6 Risk Factors Specific to CKD

The pathophysiology of secondary pulmonary hypertension in CKD patients is still complex and not completely clear(Di Lullo et al., 2013).

Pulmonary circulation impairment is observed togetherwith chronic volume overload, connective tissue diseases, acquired and congenital cardiopathies,HIV infection, hepatic cirrhosis with portal hypertension, and all chronic comorbiditieswith increased pressures in the left heart side(Di Lullo et al., 2013).

CKD patients have two peculiar clinical features: anemia and (in most of them) arteriovenous fistula; both factors lead to an increased preload on the right heart chambers(Di Lullo et al., 2013; Yigla et al., 2003).

Pulmonary hypertension can lead to increased levels of cytokines and growth factors, such as FGF, PDGF, and TGF-β, with concomitant pulmonary angiotensin-converting enzyme (ACE) activation (Di Lullo et al., 2013). As a consequence, these factors lead to abnormal smooth muscle cell proliferation and fibrosis (Bogaard et al., 2012; Wedgwood et al., 2007).

2.4.7 Endothelial Dysfunction

Endothelial dysfunction, together with a lower activation of nitric oxide synthase (NOS), increased levels of serum endothelin and fibrin storages, could involve an extensive growth of endothelial cells until complete obliteration of pulmonary vessels(Di Lullo et al., 2013).

In chronic obstructive pulmonary disease, the main mechanism underlining increased pulmonary pressure is chronic hypoxia, a potent pulmonary vasoconstrictor

If sustained, vasoconstriction in the lung leads to extensive remodeling of the pulmonary vessels and a steady reduction in vessel compliance, a phenomenon which in and of itself contributes to pulmonary hypertension (Sakao S, 2010).

Pathologic processes behind the complex vascular changes associated with PHTN include vasoconstrictor/vasodilator imbalance, thrombosis, misguided angiogenesis and inflammation.

The function of the pulmonary endothelium is altered with decreased production of vasodilators such as prostacyclin and nitric oxide and an increased production ofendothelins, finally resulting in pulmonary vascularremodeling.

2.5 Diagnosis

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death. Recently, the diagnostic approach has been more clearly defined according to the new clinical classification and with consensus reached on algorithms of various investigative tests and procedures that exclude other causes and ensure an accurate diagnosis of PAH.

The diagnosis should be suspected in patients with increasing dyspnea on exertion and a known cause of pulmonary hypertension. Two-dimensional echocardiography with Doppler flow studies is the most useful imaging modality in patients with suspected pulmonary hypertension (Hammerstingl et al., 2012; Trenton D. Nauser., 2001).

The diagnostic procedures include clinical history and physical examination, ECG, chest X-ray, transthoracic Doppler echocardiography, pulmonary function tests, arterial blood gas analysis, ventilation and perfusion lung scan, high-resolution computed tomography of the lungs, contrast-enhanced spiral computed tomography of the lungs and pulmonary angiography, blood tests and immunology, abdominal ultrasound scan, exercise capacity assessment, and hemodynamic evaluation(Trenton D. Nauser, 2001). Invasive and non-invasive markers of disease severity, either biomarkers or physiological parameters and tests that can be widely applied, have been proposed to reliably monitor the clinical course

Transthoracic Doppler echocardiography is the investigation of choice for non-invasive detection of PAH but right-heart catheterization is necessary to confirm the diagnosis of PAH and determine its mechanism. Pulmonary function tests and chest CT scan may detect an underlying chronic pulmonary disease (hypoxic PHTN). Lung perfusion scan and contrast-enhanced chest spiral CT scan can lead to the diagnosis of thromboembolic PHTN, which is to be confirmed by pulmonary angiography. Assessment of the severity of PHTN is based on clinical parameters (NYHA, right heart failure), functional tests (six-minute walk test), echocardiography and hemodynamics. Characterization of PHTN is essential in its management because it determines the appropriate treatment: an etiological treatment in passive, obstructive or hypoxemic PHTN, or vasodilator and antiproliferative therapies in PAH.

2.6 Diagnostic tools

The diagnostic procedures include clinical history and physical examination, a standard chest radiography, electrocardiography, transthoracic Doppler echocardiography, pulmonary function tests, arterial blood gas analysis, ventilation and perfusion lung scan, high-resolution computed tomography of the lungs, contrast-enhanced spiral computed tomography of the lungs and pulmonary angiography, blood tests and immunology, abdominal ultrasound scan, exercise capacity assessment, and hemodynamic evaluation.

Invasive and non-invasive markers of disease severity, either biomarkers or physiological parameter and tests that can be widely applied, have been proposed to reliably monitor the clinical course. Pulmonary biopsy is rarely indicated. Transthoracic echocardiography is a key screening tool in the diagnostic algorithm. Because transthoracic echocardiography is an inexpensive, easy, and reproducible method, it is the most commonly used noninvasive diagnostic tool to determine pulmonary arterial pressure. But it not only provides an estimate of pulmonary pressure at rest and during exercise, but it may also help to exclude any secondary causes of pulmonary hypertension, predict the prognosis, monitor the efficacy of specific therapeutic interventions, and detect the preclinical stage of the disease.PAPismeasurednon-invasivelybyDopplerechocardiography calculated using the modified Bernoulli equation (systolic PAP equals cardiac output multiplied by pulmonary vascular resistance (PVR), that is, PAP = cardiac output x PVR. Using a pulmonary artery acceleration time of 100 ms or less resulted in 78% sensitivity and 100% specificity for detection of elevated PAP.Doppler echocardiography findings correlate well with catheterization values and offer the opportunity of multiple measurements for diagnostic as well as therapeutic purposes. In an Italian study by Lanzarini et al. from 2005, pulmonary artery diastolic pressure obtained utilizing the early phase of the

tricuspid regurgitation spectral flow perform swell in terms of diagnostic ability, with high sensitivity and specificity (100% and 60%) and positive (80%) and negative predictive values (100%).

In addition, the measurement of serum markers, such as brain natriuretic peptide (BNP), are diagnostically useful and of prognostic significance. Once the diagnosis and etiology of pulmonary hypertension have been established, several parameters can predict outcome in these patients: functional class, right ventricular function, pulmonary hemodynamics, and certain laboratory parameters. Also, exercise parameters such as walking distance, peak oxygen uptake or peak systolic blood pressure can reliably predict prognosis in these patients.

Pulmonary hypertension has no pathognomonic and distinctive symptoms and signs; standard transthoracic echocardiography allows easy assessment of compliance of the right heart chambers (Di Lullo et al., 2013; Kosturakis, Goldberg, Allen, & Loeber, 1984; Niederle, Starek, Jezek, & Hes, 1988).

CHAPTER THREE: MATERIAL AND METHODS

3.1 Study Site

This study was conducted in the Renal unit and Adult Medical wards at the Moi Teaching and Referral Hospital(MTRH), which is a teaching and referral hospital located in Eldoret town of Uasin Gishu county in North Rift Region of Kenya. Eldoret town is 300 kilometers North-west of the Kenyan capital, Nairobi. MTRH is a tertiary (level 6) health facility serving as a teaching hospital for Moi University School of Medicine,

3.2 Study Population

Patients who are 18years and above with Chronic Kidney disease with or without dialysis in the renal unit and adult medical wards in MTRH.

3.3 Study Design

Cross-sectional hospital based study

3.4 Sampling and recruitment

3.4.1 Sampling Technique

Consecutive sampling was employed. Known CKD patients were recruited as they came to the hospital if they met the inclusion criteria. Other participants were recruited if they got diagnosed with CKD while in the ward.

3.4.2 Eligibility Criteria

3.4.2.1 Inclusion Criteria

1. Patients 18 years and above admitted to the general medical wards and the renal ward with CKD.
2. Informed consent from the patient

3.4.2.2 Exclusion Criteria

1. Patients with known cardiac disease
2. Smoking history.
3. Patients with known collagen vascular diseases
4. Previous treatment for pulmonary embolism

3.4.3 Sample size determination

The sample size required in order to be 95% sure that the proportion of the CKD patients with pulmonary hypertension was within plus or minus 5% of the population proportion of9 % (Bolignano et.al 2013) was derived using the Fisher et al, (1998) formulae:

- SAMPLE SIZE CALCULATION
  - Fisher's formula-
    - $n = \frac{Z^2P(1-P)}{e^2}$

Where n= sample size

Z= 1.96 (Confidence Interval of 95%)

P= 9% or 0.09(This was based on a study by Bolignano et.al which found a prevalence of 9%).Where n is the minimum sample size that can be collected. This means that any number greater than this can be sampled provided that it does not amount to unnecessary harm of the patients or unnecessarily inflated cost of research

e= 0.05(Margin of Error)

Therefore n = 126

3.5 Study Procedure

Potential participants presenting for care at theRenal Unit and Medical wards were screened by the Research assistant and the Principal Investigator by reviewing their medical charts. The principal investigator reviewed the sampled charts and approached the identified patients. Those who met the inclusion criteria had their consent obtained.The patients' self-reported bio data and a comprehensive medical history of current and past illnesses, including but not limited to: history of hypertension, history of diabetes, stroke, alcohol use and cigarette smoking as well as medication use including hypertension medication and drugs for diabetes being used.Blood pressure measurement was done after a patient had rested for at least 5 minutes. Two readings were taken and the average was recorded in the questionnaire (Appendix IV). Patient's weight was taken and recorded to the nearest half kilograms (kg) using a standard weighing scale which was calibrated regularly with the patients dressed in light clothing and without shoes. Patients who reported history of diabetes, was verified from the records. Blood samples were then taken for hemoglobin, hematocrit, BUN, creatinine, potassium phosphate and calcium levels, albumin, AST and ALT levels, HIV test and RBS (Appendix V and VI).Estimated Glomerular Filtration Rate(eGFR) was calculated using the CKDEPI formula(Appendix VII). Patients who were on dialysis proceeded with the procedure while those not on dialysis proceeded for

Echocardiography (Appendix VIII). Doppler echocardiography was performed on all patients. It was done within 4hours after completion of hemodialysis to avoid overestimation of systolic PAP due to volume overload while those not on dialysis it was done after consent and examination.Two trained,experienced and dedicatedoperators with assistance of the principal investigator performed all echocardiographic studies using the Machine – Phillips Xmatrix (Made in USA), Probe- Adult S5-1 .The machine is manufactured by Philips health care a part of Royal Philips Electronics, 22100 Bothel-Everett Highway Bothel, WA 98021-8431 USA. The medical device meets the provisions of the transposition of the medical device directive 93/42/EEC within the country of origin of the notified body concerned with the device. The Philips ultrasound may be manufactured under or operated in accordance with one or more of the US patents and corresponding patents in other countries. Patients were triaged and the procedure explained to them. Two-dimensional and M-mode echocardiography was performed. A tricuspid systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler probe. Systolic right ventricular pressure (or PAP) was calculated using the Bernoulli equation: PAP = 4 × (tricuspid systolic jet)^2 + 10 mm Hg (estimated right atrial pressure) . CO was estimated from the left ventricular outflow tract velocity time integral × diameter. Ejection fraction was calculated using the modified Simpson method.

For determining volume overload, the vena cava index (VCI) was evaluated. This was calculated from diameters of inferior vena cava (IVC) in expiration and inspiration (IVC diameter in expiration – IVC diameter in inspiration/IVC diameter in expiration). Isovolumetric relaxation time (IVRT) was measured from mitral inflow to show the diastolic performance. Other echocardiographic values such as E velocity, A velocity, diameter of the right atrium, right ventricular and left atrium, diastolic and systolic diameter of the left ventricle, and diastolic and

systolic volume were measured as well.For those patients on dialysis echocardiography was done within 4hours of post dialysis. All laboratory investigations were carried out at the MTRH laboratory according to good laboratory and clinical guidelines/practices. The procedures were carried out by the principal investigator, research assistant and a trained laboratory technician and echo cardiographer.

The principal investigator interviewed the patients and recorded a detailed medical history, physical findings and drew blood for the various laboratory tests.

The research assistant facilitated triage of the patients and took blood samples to the laboratory for analysis and followed up laboratory results.

Trained laboratory technician carried out the laboratory tests as per the required standards and regulations. The trained echo cardiographer performed the Doppler echocardiography with the assistance of the principle investigator. The final diagnosis of presence of PHTN or no PHTN was made by estimations using Doppler echocardiography and SPAP > 35mmHg was regarded as PHTN.

3.6 Data collection tools and management

3.6.1Data collection

Data was collected between January and September 2015, using interviewer administered structured questionnaire (Appendix I). The data collection tool was validated by monitoring the data trends during data collection. Data cleaning included scrutinizing completed forms for inconsistencies, errors and omissions. Defective forms were immediately returned to the principal investigator for correction. Patients fulfilling the inclusion criteria were recruited and enrolled by the principal investigator. Medical records were also reviewed and relevant clinical

and laboratory data were obtained and entered into the data collection form. The variables collected included demographic characteristics such as age, gender, history of smoking, alcohol use, and occupation. Medical history of hypertension, diabetes and kidney disease were also obtained

3.6.2 Enrollment of participants

At the Renal unit and medical wards, subjects aged more than 18 years were screened for detection of CKD for 3 or more months as diagnosed by the primary clinician. Estimated Glomerular Filtration Rate (eGFR) was used as an estimate of renal dysfunction and those with eGFR less than 90ml/min were considered as CKD.The subjects were interviewed with help of appropriate schedule to elicit information regarding their socio demographic characteristics, behavioral parameters and disease related parameters and whether they were on dialysis or not. Blood samples were taken for analysis of Blood Urea Nitrogen (BUN), Creatinine levels, Potassium levels, Albumin levels,Hemoglobin levels, Calcium and Phosphate levels, hematocrit, random blood sugar.They were then taken for echocardiography immediately for those not on dialysis or within 4 hours post dialysis for those on dialysis.

3.6.3 Data Management

Data was entered into excel database. It was de –identified and encrypted. Pass word was only known to the principle investigator. Database was also backed up for recovery when necessary.

After data entry the questionnaires were kept in a cabinet and locked.

3.6.4 Data Analysis and Presentation

Data analysis was done using STATA version 13 special edition. Categorical variables were summarized as frequencies and corresponding percentages. Continuous variables that assumed Gaussian distribution were summarized as mean and the corresponding standard deviation

(SD).Continuous variable that violated the Gaussian assumptions were summarized as median and the corresponding inter quartile range (IQR). Inferential statistics were used to draw conclusions about the population. Significance tests such as the two-sample t-test for comparison of two normally distributed continuous variables, two-sample Wilcoxon rank sum test (aka Mann Whitney U test) for non-Gaussian distributed continuous variables, and Pearson's Chi Square test for categorical variables were used.. Statistical significance was defined as $P \leq 0.05$.

3.7 Ethical consideration

This study was carried out with the approval of the Institutional Research and Ethics Committee (IREC) of MTRH and Moi University School of Medicine and permission from MRTH management. A signed written informed consent was obtained for each participant who was included in this study (Appendix II). Confidentiality was maintained throughout the study by pass-word protecting the database and limiting its access only to principal investigator and research assistants. Interviews were carried out in a consultation room to ensure privacy and convenience. All participants including those who declined consent received the same level of care awarded to all other patients irrespective of their participation. There were very minimal anticipated risks to the participants attributable to this study except the physical pain and discomfort associated with sample collection. Questionnaires will be shredded after three years or publication of the study findings. There was no conflict of interest in this study and no incentives were used to recruit patients. Patients were informed of their results and the same availed to their primary clinicians. This thesis shall be availed at the MUSOM library. It will also be published in a reputable journal and presented in professional conferences and seminars.

3.8 Dissemination of results

The results of the study will be disseminated through a written thesis and an oral defense in a forum that shall be convened by the school of medicine. The results will also be shared with MTRH and published in peer-reviewed journal.

CHAPTER FOUR: RESULTS

A total of 233 participants were screened for eligibility into the study. Of these, 132 were successfully consented and enrolled. The remainder were excluded from the study for various reasons as shown in **Figure 1**

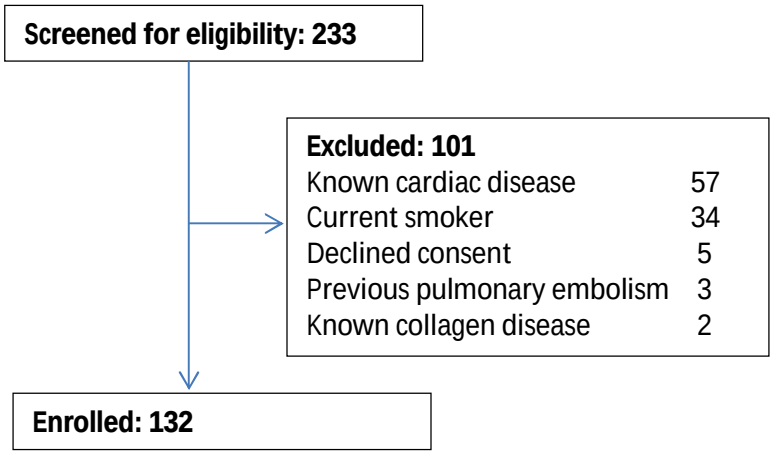

Figure 1: Study flow chart

Among the 132 participants included in the final analysis, 82(62%) were male, median age 47 years (IQR 31-59). Only 8% and 2% of the participants reported current history of alcohol use and smoking respectively. Other social-demographic characteristics are summarized in **Table 1**and in **Figure 2**

Table 1: summary of social-demographic characteristics

Variable	n	Median (IQR); proportion
Age(years)	**132**	**47 (31-59)**
Gender	**132**	
Male	**82**	**62%**
Female	**50**	**38%**
Occupation	**132**	
Farmer	**44**	**33%**
Housewife	**29**	**22%**
Student	**17**	**13%**
Other	**42**	**32%**
Alcohol use	**132**	
Yes	**10**	**8%**
No	**122**	**92%**
Smoking	**131**	
Yes	**3**	**2%**
No	**128**	**98%**
Type of fuel	**132**	
Charcoal	**23**	**17%**
Firewood	**107**	**81%**
Gas	**2**	**2%**

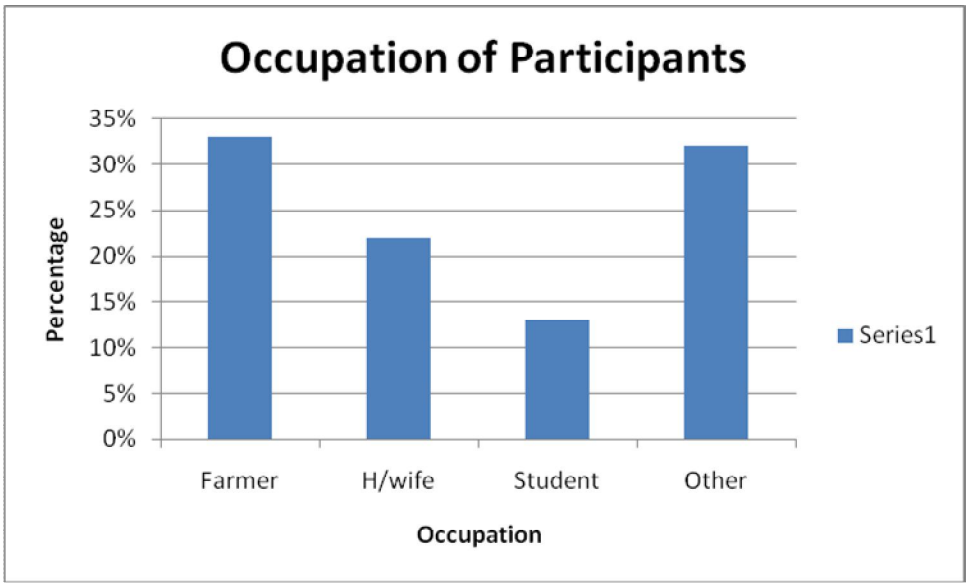

Figure 2: Occupation of Participants

Table 2 summarizes clinical characteristics of the included participants. As illustrated, majority (82%) of the participants were hypertensive with a median blood pressure of 150/90 mmHg (IQR 131/75-168/100). An estimated 81% of the participants reported using antihypertensive medication. An estimated 28% of the participants were diabetic, with approximately 15% and 11 % being on oral hypoglycemics and insulin respectively. Majority of the participants (78%) were on dialysis, with most (71%) having only one session of dialysis per week. The most common venous access site was subclavian/internal jugular catheter (87%), compared with arteriovenous fistula (11%) and tunneled catheter (2%) respectively (**Figure 3**).

Table 2: Summary of clinical characteristics

Variable	n	Median (IQR); proportion (%)
Blood pressure (mmHg)	**132**	**150/90(131/75-168/100)**
Weight (Kg)	**132**	**65 (59-75)**
Pulse oximeter (spo2%) **1 ≥95%** **2 90-94%** **3 <90%**	**132** **103** **19** **10**	 **78%** **14%** **8%**
Hypertensive **Yes** **No**	**132** **109** **23**	 **82%** **18%**
Diabetes mellitus **Yes** **No**	**132** **37** **95**	 **28%** **72%**
HIV status **Positive** **Negative**	**132** **13** **119**	 **10%** **90%**
Asthmatic **Yes** **No**	**132** **1** **131**	 **1%** **99%**
Chronic Lung disease **Yes** **No**	**132** **7** **125**	 **5%** **95%**
On Dialysis **Yes** **No**	**132** **102** **30**	 **78%** **22%**
Dialysis Mode **1 Hemodialysis** **2 Peritoneal**	**102** **100** **2**	 **98%** **2%**
Dialysis frequency **1. Once/wk** **2. Twice/wk** **3. Other**	**102** **72** **27** **3**	 **71%** **26%** **3%**
Onset of dialysis (Months)	**102**	**7 (2-12)**
On antihypertensives **Yes** **No**	**132** **107** **25**	 **81%** **19%**
On Oral hypoglycemic **Yes** **No**	**132** **21** **111**	 **16%** **84%**
On Insulin **Yes**	**132** **14**	 **11%**

No	**118**	**89%**
Venous Access **1 AV fistula** **2 subclavian/Jugular** **3 Perm catheter**	**102** **11** **89** **2**	 **11%** **87%** **2%**
Pulmonary Hypertension **Yes** **No**	**132** **70** **62**	 **53%** **47%**
RVSP (mmHg)	**132**	**41 (37-53)**

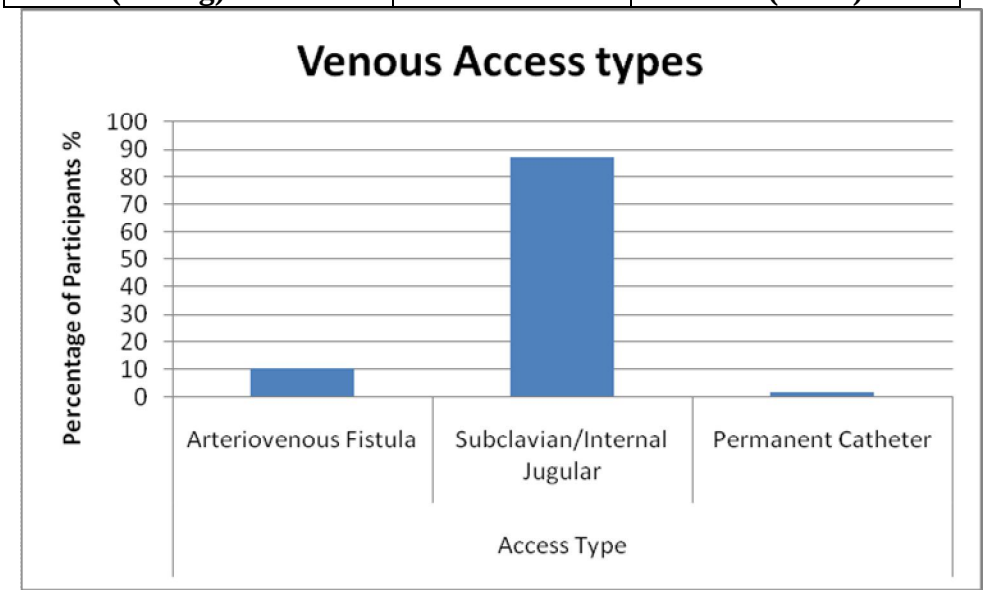

Figure 3: Dialysis Access Points

The prevalence of pulmonary hypertension among patients with chronic kidney disease was 53% (95%CI 43-61). Among those with pulmonary hypertension, the median right ventricular systolic pressure (RVSP) was 50 mmHg (IQR 40-58). As illustrated in **Figure 4**, an estimated 90% of participants with pulmonary hypertension were on dialysis.

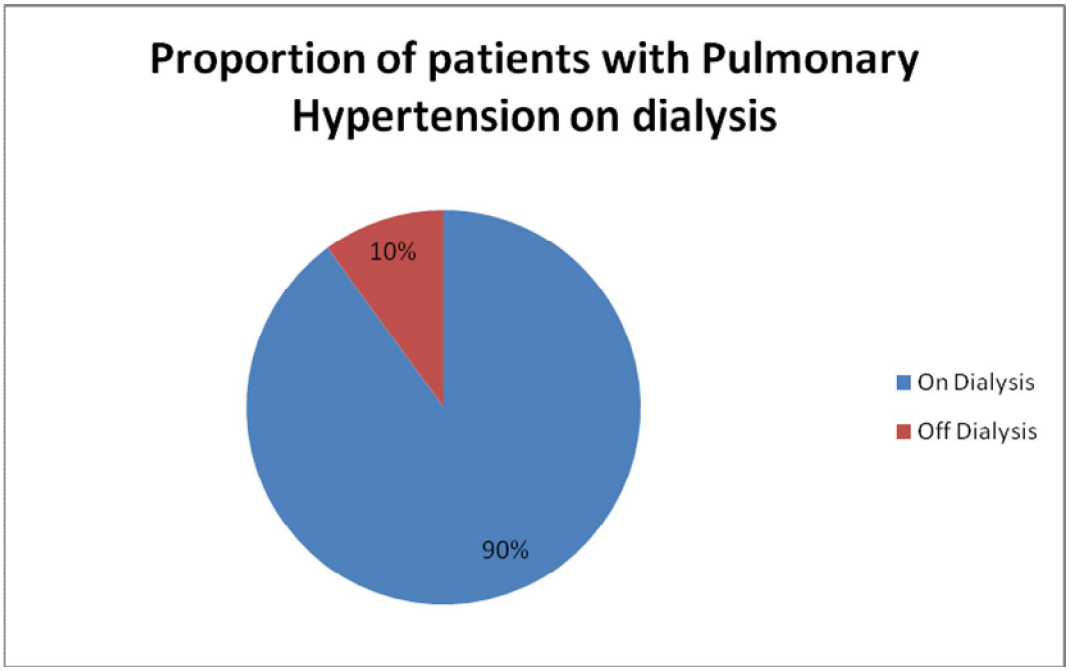

Figure 4: Pie Chart: Proportion of patients with Pulmonary Hypertension on dialysis

Table 3 is a summary of pertinent laboratory parameters for the included participants. As shown, the mean hemoglobin was 8.5g/dL (sd 2) with a median hematocrit of 24.8 (sd 6). Of note nearly 40% of the participants had an elevated serum potassium level, with an estimated 10% having grade 4 hyperkalemia of ≥7.0. Similarly, close to 40% of the participants had hypocalcemia (corrected for the level of hypoalbuminemia). The median eGFR computed using the CKD EPI formula was 5 ml/min/1.73m^2 (IQR 3-8).

Table 3: Summary of Laboratory Parameters

Variable	n=132	Mean (sd);Median (IQR); proportion %
Hemoglobin(g/dl)	132	8.5 (2.0)
Hematocrit (%)	132	24.8 (6.0)
Albumin(g/L)	132	32 (6.6)
AST (U)	132	18.9(14-22)
ALT	132	17(13-21)
K+(mmol/L)		
Grade 0 (≤5.5)	82	62%
Grade 1 (5.6-5.9)	13	10%
Grade 2 (6.0-6.4)	17	13%
Grade 3 (6.5-6.9)	12	9%
Grade 4 (≥7.0)	8	6%
***Corrected Ca++**		
Grade 0 (>2.09)	83	63%
Grade 1 (1.95-2.09)	12	9%
Grade 2 (1.75-1.94)	14	11%
Grade 3 (1.53-1.74)	13	10%
Grade 4 (<1.53)	10	7%
Po4-	132	2.28(1.56-3.11)
RBS (mmol/L)	132	5.7(4.9-6.7)
BUN (mmol/L)	132	34(25-45)
Serum creatinine (ummol/L)	132	1003(649-1584)
eGFRCKDEPI (ml/min/1.73m^2)	132	5(3-8)

*Corrected Ca++ computed based on the level of hypoalbuminemia as per the equation below
Corrected Ca++= serum Ca++ (mmol/L) + 0.02(40-albumin g/L)

Table 4 is a cross tabulation of pulmonary hypertension and dialysis status of the patients. Overall 70 participants (53%) had pulmonary hypertension. The Prevalence of pulmonary hypertension was higher among participants on dialysis 63/100 (63%) compared to those not on dialysis is 7/32 (22%). Patients on dialysis had higher odds of having pulmonary hypertension (OR 5.9; 95%CI 2.4-15.2; p 0.0001) compared with patients not on dialysis

Table 4: Cross-tabulation of Pulmonary Hypertension and Dialysis

	Dialysis		
Pulmonary HTN	**No**	**Yes**	**Total**
No	25	37	**62**
Yes	7	63	**70**
Total	**32**	**100**	**132**

We assessed the duration since patients had started on dialysis to the time of study and its impact on RVSP. There was marginally higher RVSP for every month one had been on dialysis (coefficient 0.28 mmHg; 95%CI -0.06 to 0.6; p 0.11). However, this difference did not attain statistical significance.

RVSP (Right Ventricular Systolic Pressure)	**Coefficient (95% CI)**	**P value**
Duration on Dialysis	0.29(-0.06-0.63)	0.108

In the univariate model, we assessed the association between pulmonary hypertension and potential risk factors selected a priori. These included hemoglobin/hematocrit levels; systemic hypertension, diabetes mellitus, HIV status, calcium levels, intravenous access types, dialysis status, duration on dialysis since onset, smoking history and use of medicines including insulin,

anti-hypertensives and oral hypoglycemics. As illustrated in **Table 5**, being on dialysis conferred increased odds of having pulmonary hypertension (OR 5.98; 95%CI 2.35-15.19; p 0.0001). All other factors assessed were not significantly associated with pulmonary hypertension.

Similarly, in the multivariate analysis (**Table 6**), being on dialysis was significantly associated with pulmonary hypertension (adjusted OR7.09; 95%CI 2.60-19.40; p 0.0001)

Table 5: univariate (unadjusted)model of factors associated with pulmonary hypertension

Variable	**Odds ratio(95% CI)**	**P-value**
Hemoglobin	1.16(0.97-1.38)	0.101
Hematocrit	1.03(0.97-109)	0.368
Hypertension	1.94(0.78-4.88)	0.156
Antihypertensive	1.53(0.64-3.69)	0.336
Diabetes	0.93(0.43-1.99)	0.849
Insulin	0.36(0.11-1.24)	0.106
Oral hypoglycemic	1.56(0.60-4.07)	0.358
Dialysis	**5.98(2.36-15.19)**	**0.0001**
Duration on dialysis	1.02(0.98-1.06)	0.369
HIV positive	0.36(0.10-1.24)	0.106
Serum Calcium	0.98(0.93-1.04)	0.525
IV access **Subclavian/jugular** **AVF**	 2.14(0.60-7.56) 1	 0.239
Smoking history	1.84(0.16-20.90)	0.620
Potassium	1.28(0.93- 1.75)	0.117
Phosphate	1.04(0.75- 1.44)	0.798
BUN	0.76(0.33- 1.71)	0.510
Creatinine	1.00(0.99- 1.00)	0.564
Age	0.99(0.97- 1.01)	0.738
Weight	0.97(0.93- 1.00)	0.111
Male	1.79(0.86- 3.58)	0.120

Table 6: Multivariate Model of factors associated with pulmonary hypertension

Variable	Odds ratio(95% CI)	P-value
Dialysis	**7.09(2.60-19.40)**	**0.0001**
Hemoglobin	1.28(0.91-1.80)	0.163
Hematocrit	0.96(0.86-1.08)	0.498
HIV positive	0.25(0.06-1.03)	0.060
Diabetes	0.70(0.08-5.78)	0.743
Insulin	0.55(0.05-5.75)	0.620
Oral hypoglycemics	1.99(0.211-18.75)	0.547
Hypertension	0.86(0.27-2.78)	0.805
Calcium	0.97(0.91-1.05)	0.483
Smoking history	0.77(0.06-9.77)	0.844
Potassium	1.107(0.77-1.58)	0.575

Table 7: Correlation of Variables between patients with and without pulmonary hypertension

Variable	Without PHTN n (%); mean(sd)	With PHTN n (%);mean(sd)	Odds Ratio(95% CI)	P Value
Dialysis **No** **Yes**	 **25(40%)** **37 (60%)**	 **7(10%)** **62(90%)**	**5.98(2.36-15.19)**	**0.0001**
Gender **Female** **Male**	 28(45%) 22(32%)	 34(55%) 47(68%)	1.79(0.86- 3.58)	0.118
Age(years)	46.7(16.6)	45.2(16.4)	0.99(0.97- 1.01)	0.740
Weight(Kg)	66.4(10.7)	63.6(9.5)	0.97(0.93- 1.00)	0.108
Hb(g/dl)	8.2(2.0)	8.8(1.9)	1.16(0.97-1.38)	0.099
Hct (%)	24.3(6.5)	25.2(5.6)	1.03(0.97-109)	0.370
Ca(mmol/l)	5.0(24.3)	2.1(0.5)	0.97(0.91-1.05)	0.326
K(mmol/l)	5.2(1.2)	5.5(1.2)	1.107(0.77-1.58)	0.111
Po4(mmol/l)	2.4(0.9)	2.4(1.1)	1.04(0.75- 1.44)	0.799
BUN(mmol/l)	35.2(16.7)	38.3(18.1)	0.76(0.33- 1.71)	0.315
Cr(mmol/l)	1142.8(736.1)	1214(683.3)	1.00(0.99- 1.00)	0.566

Table 8: Description of variables seen in patients with and without dialysis

Variable	**With Dialysis n(%); mean(sd)**	**Without Dialysis n(%); mean(sd)**	**Odds Ratio(95%CI)**	**P-Value**
PHTN No Yes	 25(78%) 7(22%)	 37(37%) 63(63%)	 5.98(2.39-14.86)	 **0.0001**
Gender **Female** **Male**	 15(47%) 17 (53%)	 35(35%) 64(65%)	 1.61(0.72-3.58)	 0.243
Age(years)	49.9 (sd 16.3)	44.9 (sd 16.3)	0.98(0.95-1.00)	0.135
Weight(Kg)	66.9 (sd 10.5)	64.3(sd 9.9)	0.97(0.94-1.01)	0.211
Hb(g/dl)	8.48 (sd 2.0)	8.52(sd 1.9)	1.01(0.83-1.23)	0.992
Hct (%)	24.81(sd 7.2)	24.78(sd5.6)	0.99(0.94-107)	0.983
Ca(mmol/l)	1.90 (sd 0.58)	2.08 (sd0.47)	2.24(0.91-5.53)	0.80
K(mmol/l)	5.15 (sd 1.1)	5.50(sd 1.2)	1.33(0.90-1.95)	0.145
Po4(mmol/l)	2.39 (sd 0.9)	2.48(sd 1.1)	1.09(0.74-1.59)	0.670
BUN(mmol/l)	36.49 (sd 16)	37.03 (sd 18)	1.00(0.98-1.02)	0.878
Cr(mmol/l)	1009 (sd 735)	1235 (635)	1.00(0.99-1.00)	0.119

CHAPTER FIVE: DISCUSSION

5.1 Prevalence of Pulmonary hypertension in CKD

Pulmonary hypertension is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology(Emara et.al 2013). Its presence in CKD has been recently suggested to occur in considerable portions of patients and has been associated with a worse outcome(Kosmadakis et.al 2013).During the last two decades evidence has accrued documenting that mild to moderate forms of pulmonary hypertension are much more common than traditionally has been thought (Simonneau G et.al 2009). These forms often remain undetected because the disease has along preclinical asymptomatic phase and PHTN is suspected only when the clinical signs and symptoms of right ventricular dysfunction, namely progressively worsening fatigue, dyspnea, and syncope are manifest (Budesch DB et.al 2009). The prevalence of chronic kidney disease (CKD) in the developed world is 13% and is recognized as a condition that elevates the risk of cardiovascular complications as well as kidney failure and other complications(J. Coresh & 2007).The mean annual incidence of PHTN in the general population is 15.9 new cases per million citizens per year, and the mean prevalence is 15–50 cases per million populations.The prevalence of pulmonary hypertension ranges from 9%-39% in individuals with stage 5 CKD, 18.8%-68.8% in hemodialysis patients, and 0%-42% in patients on peritoneal dialysis therapy (Bolignano et.al 2013).Chronic kidney disease substantially increases the risk of death, cardiovascular disease, and use of specialized health care(S. Pabst, 2015). However, Yigla et al. first noted unexplained PHTN in some long-term hemodialysis (HD) patients during an epidemiologic study.Both CKD and long-term hemodialysis via arteriovenous fistula may be involved in the pathogenesis of pulmonary hypertension by affecting pulmonary vascular resistance and cardiac output.Hormonal and

metabolic derangement associated with end-stage renal disease might lead to pulmonary arterial vasoconstriction and an increase in pulmonary vascular resistance (Yigla et.al 2003).

Therefore in this study, we sought to investigate the prevalence of PHTN in CKD and describe the associated clinical correlates. The prevalence of PHTN in this study was 53% among the CKD patients. This was a high prevalence and could be attributed to majority of our respondents were on hemodialysis which has been associated with development of PHTN in the longrun.The prevalence of pulmonary hypertension in dialysis patients is relatively high and varies in different studies from 17% to 49.53% depending on the mode of dialysis and other selection factors, such as the presence of other cardiovascular comorbidities(Kosmadakiset.al 2013). A systematic review done by Bolignano and team showed a prevalence of 18.8% – 48.8% in patients on hemodialysis. The range in values is attributable to the difference in methodology and cut off points in the different studies for diagnosing PHTN. This is comparable with our study which showed a prevalence of 53%.This can be attributed to a similar study population group of CKD patients with the majority of them being on hemodialysis. The slight difference in the wide range of prevalence could be attributed to a difference in methodology in which our study excluded most patients with comorbidities and we did not discriminate on the duration since the patient had been on dialysis whereas Bolignano in his study enrolled patients who had been on dialysis for more than 6 months.A study done by (Emara et. al 2013) in Saudi Arabia demonstrated a high prevalence of pulmonary hypertension (SPAP > 35 mmHg) among 27 patients (41.53%) receiving long-term hemodialysis with a mean systolic SPAP of 49.33 ± 9.18 mmHg. This is comparable with our study which showed a median right ventricular systolic pressure (RVSP) of 50 mmHg (IQR 40-58) among those with pulmonary hypertension on hemodialysis. This could be attributed to the same methodology in which majority of the

patients included in the study were on hemodialysis similar to the study by Emara. The slight variation in the prevalence could be attributed to longer duration on dialysis in the Emara study group with a dialysis vintage of more than 6 months and all their patients were on AVF as a mode of venous access compared to our study in whichmajorities were on temporary venous access for dialysis.

Similarly our finding of a prevalence of 53% was in accordance with (Domenici et al., 2010) who reported that Pulmonary hypertension was found in 23/39 (58.9%) of the HD patients and 2/9 (22.2%) of the PD patients; PAP was significantly higher in HD patients than in PD patients ($P < 0.01$). This could be attributed to a majority of their participants being on hemodialysis similar to our study.The lower prevalence of pulmonary hypertension in patients on peritoneal dialysisin the study by Domenici compared to this study could be explained by the low number of patients on PD in our study 2 versus 9 respectively. Also (Patel et al. 2007)demonstrated that forty-one patients had pulmonary hypertension, of which 33% were on hemodialysis. This was slightly different from this study perhaps because of difference in the study population group and methodology. Also(Yigla et al.2003) reported that SPAP > 35 mmHg was found in 39.7% of patients receiving hemodialysis (mean ± SD, 44 ± 7 mmHg; range, 37 to 65 mmHg) and none in patients receiving PD.This was also comparable with our study in which only one of the patients on peritoneal dialysis had SPAP> 35mmHg.However, this might not reflect an accurate comparison because we had a much less number of patients on dialysis in our study compared to the Yigla study. Similarly, (Fabbian et al. 2011)demonstrated that PHTN (PAP > 35 mmHg) was detected in 22 patients (39%; PAP 42 ± 6 mmHg) and was diagnosed in 18.5% of PD patients and 58.6% of HD patients ($P = 0.021$). This was slightly different from our finding of 50% on PD patients because one out of the two patients on PD had SPAP>35mmHg, however the

findings were comparable for those on HD.In a study done by L. Kumbar, the prevalence of pulmonary hypertension among patients on peritoneal dialysis was 42% with a mean age (+/- SD) of(58+/- 15yrs).(L. Kumbar, 2007). This was comparable to our study which found a prevalence of 50%, however there were only 2 patients in our study compared to their study which had 36 patients. Also (Mahdavi-Mazdeh et al. 2008) reported that prevalence of PHTN ranges from 30–40% as detected by Doppler echocardiography in patients on chronic hemodialysis (HD) therapy. In another study (Abdelwhab and Elshinnawy, 2008) demonstrated that PHTN was found in 44.4% of patients on Hemodialysis, this too was comparable to our study.A study by Soki et. al at Kenyatta National Hospital in Nairobi, Kenya showed a prevalence of PH among CKD patients of 32.5%, with a median SPAP of 47.3mmHg and a range of 36.1–79 mmHg. A strong association between PH and ejection fraction of less than 50%, as a marker of LV dysfunction, was demonstrated (Soki et.al., 2017). This was slightly different from our study and this could be attributed to a longer dialysis vintage of more than 13years compared to our shorter dialysis vintage of a median of 7 months and probably a more adequate dialysis at Kenyatta National Hospital. An exclusion of fluid overloaded patients in the Soki study could also account for a lower prevalence of PHTN since fluid overload is a known associate of pulmonary hypertension.

In this studythe prevalence of pulmonary hypertension was higher among participants on dialysis 63/100 (63%) compared to those not on dialysis 7/32 (22%). This was comparable to the study by Patel et.al 2007 which showed a higher prevalence of PHTN in those patients on dialysis compared to those who were on conservative management.We assessed the impact duration since on dialysis had on RVSP. There was marginally higher RVSP for every month longer on

dialysis (coefficient 0.28 mmHg; 95%CI -0.06 to 0.6; p 0.11). However, this difference did not attain statistical significance.

An estimated 63/70(90%) of participants with pulmonary hypertension were on dialysis and the median right ventricular systolic pressure (RVSP) was 50 mmHg (IQR 40-58). A study by (Abdallah et al. 2010) demonstrated that PHTN (systolic PAP = 35 mmHg) was observed in 25 (56.8%) patients receiving hemodialysis with a mean systolic PAP of 46.4 ± 13.6 mmHg. This was different from our study because they used a smaller number of respondents and their respondents were at least on twice weekly hemodialysis compared to the once weekly dialysis in this study. The once weekly dialysis was majorly reported to be due to constraints in resources. It has been found that repeated episodes of hypoxia during and/or after HD lead to the development of pulmonary hypertension and cause morphological changes in the lung(H. Igarishi, 1985; M.P. Dhakal & 1999; N.M. Aurigemma, 1977).

5.2 Clinical correlates associated with PHTN in CKD

We assessed the association between pulmonary hypertension and potential risk factors selected a priori. These included hemoglobin/hematocrit levels; systemic hypertension, diabetes mellitus, HIV status, calcium levels, intravenous access types, dialysis status, duration on dialysis since onset, smoking history and use of medicines including insulin, anti-hypertensives and oral hypoglycemics. Being on dialysis conferred increased odds of having pulmonary hypertension (OR 5.98; 95%CI 2.35-15.19; p 0.0001).This was comparable with a study done by Emara et .al 2013 which found a statistically significance odd of having pulmonary hypertension if on hemodialysis with SPAP of 36.15 ± 13. 24 ($P < 0.05$).

Emara et. al found a statistical significance association of having pulmonary hypertension with a longer duration of hemodialysis94 ± 10.54 ($P < 0.001$) .In contrast our study found a positive

correlation however, did not achieve statistical significance of having pulmonary hypertension with longer duration of hemodialysis1.02(0.98-1.06) ($p<0.369$). This could be attributed to the longer duration of dialysis in their study group (> 6 months)compared to the shorter duration in our study group which included patients who had undergone dialysis for 1 month only . Furthermore, we did not do a follow up to establish this spatial relationship between longer duration on dialysis and development of pulmonary hypertension.All other factors assessed were not significantly associated with pulmonary hypertension. This was in contrast to Emara et. al study which showed statistical significance in hemoglobin and hematocrit reduction and also on serum calcium level in relationship to SPAP elevation in hemodialysis. However, Amin et. al 2003 reported that there was no significant difference between patients with PHTN and those without PHTN in CKD patients, who were receiving regular hemodialysis with regard to age, duration of dialysis andserum calcium. This was similar to our study findings.

5.3 Study Limitation

This study has certain limitations. The exclusion criteria used in our protocol resulted in a smaller study group, since the majority of patients with CKD had concomitant cardiac or pulmonary disease. The exclusion of patients with CKD with cardiac or pulmonary disease from analysis was a methodological necessity to minimize confounders as much as there wasn't an intension to establish causality. Moreover, PAP was measured by a non-invasive method, trans-thoracicDoppler echocardiography, without obtaining direct invasive measurements (e.g. right heart catheterization) which is the gold standard.However, measurements of PAP by the applied Doppler echocardiographic method have been reported to have a good correlation with measurements obtained by invasive methods in some studies(H.W. Farber, 2011; J. Etemadi, 2011; S. Marangoni, 1988).This method of PAP measurement has been widely applied in previous studies on PHTN in patients on HD or PD.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1. The prevalence of pulmonary hypertension in CKD patients is high in MTRH.
2. The prevalence of pulmonary hypertension in CKD patients on dialysis is higher compared to that of patients not on dialysis at MTRH.
3. The clinical characteristics seen among patients with and without PHTN in CKD were not significantly different.

6.2 Recommendations

Pulmonary hypertension is not only a reality in our hemodialysis patients but also appears as a major problem due to its high prevalence hence early detection through screening is needed for adequate care which is the only way to prevent the progress of pulmonary hypertension.

Since follow-up duration of this study was not long enough to evaluate the effect of PHTN on morbidity and mortality, long-term follow-up of patients with PHTN is needed.

REFERENCES

Abassi Z, N. F., Khankin E, Reisner SA, Yigla M. . (2006). Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. Current Opinion in Nephrology and Hypertension., 15, 353–360.

AM, E. (2011). Hypoxic pulmonary vasoconstriction: mechanisms of oxygen-sensing. Current Opinion in Anaesthesiology. 24, 13–20

Amin M, F. A., Hamid MA, Elhendy A:. (2003;). Pulmonary hypertension in patients with chronic renal failure: role of parathyroid hormone and pulmonary artery calcifications. Chest, 124, 2093–2097.

Badesch, D. B., Champion, H. C., Gomez Sanchez, M. A., Hoeper, M. M., Loyd, J. E., Manes, A., . . . Torbicki, A. (2009). Diagnosis and Assessment of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology, 54(1s1), S55-S66. doi: 10.1016/j.jacc.2009.04.011

Barceló A, d. l. P. M., Ayllón O, . . (2009). Increased plasma levels of asymmetric dimethylarginine and soluble CD40 ligand in patients with sleep apnea. Respiratory Medical journal., 77, 85–90.

Bendayan D, B. Y., Kramer MR: . (2000). Pulmonary calcifications: a review. Respiratory Medical journal, 94, 190–193.

Bogaard, H. J., Al Husseini, A., Farkas, L., Farkas, D., Gomez-Arroyo, J., Abbate, A., & Voelkel, N. F. (2012). Severe pulmonary hypertension: The role of metabolic and endocrine disorders. Pulmonary Circulatory journal, 2(2), 148-154. doi: 10.4103/2045-8932.97592

Bolignano, D., Rastelli, S., Agarwal, R., Fliser, D., Massy, Z., Ortiz, A., . . . Zoccali, C. (2013). Pulmonary hypertension in CKD. American Journal of Kidney Disease, 61(4), 612-622. doi: 10.1053/j.ajkd.2012.07.029

Bozbas, S. S., Akcay, S., Altin, C., Bozbas, H., Karacaglar, E., Kanyilmaz, S., . . . Haberal, M. (2009). Pulmonary hypertension in patients with end-stage renal disease undergoing renal transplantation. Transplant Procedure journal, 41(7), 2753-2756. doi: 10.1016/j.transproceed.2009.07.049

Chan ED, M. D., Welsh CH, McDermott MT, Schwarz MI: . (2002;). Calcium deposition with or without bone formation in the lung. American Journal of Respiratory Critical Care Medicine, 165, 1654–1669.

Conger JD, H. W., Alfrey AC, Contiguglia SR, Stanford RE, Huffer WE: . (1975). Pulmonary calcification in chronic dialysis patients. Clinical and pathologic studies. . Annals of Internal Medicine, 83, 330–336.

Craddock PR, F. J., Brigham KL, Kronenberg RS, Jacob HS. (1977). Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. New England Journal of Medicine, 296, 769–774.

Craddock PR, F. J., Dalmasso AP, Brigham KL, Jacob HSJ (1977). Hemodialysis leucopenia. . Clinical Investigation journal, 59, 879–888.

Di Lullo, L., Floccari, F., Rivera, R., Barbera, V., Granata, A., Otranto, G., . . . Ronco, C. (2013). Pulmonary Hypertension and Right Heart Failure in Chronic Kidney Disease: New Challenge for 21st-Century Cardionephrologists. Cardiorenal Medical journal, 3(2), 96-103. doi: 10.1159/000350952

DNS:, K. (1997). Hypercalcemia and metastatic calcification. Cardiovascular and Respiratory medical journal, 36, 293–297.

DP:, B. (1996). Role of endothelin in renal function and dysfunction. Clinical Experiment on Pharmacology and Physiology medicine, 23, 345–349.

El-Shafey, E. M., El-Nagar, G. F., Selim, M. F., El-Sorogy, H. A., & Sabry, A. A. (2008). Is there a role for endothelin-1 in the hemodynamic changes during hemodialysis? Clinical and Experimental Nephrology, 12(5), 370-375. doi: 10.1007/s10157-008-0065-2

Emara, M. M., Habeb, M. A., Alnahal, A. A., Elshazly, T. A., Alatawi, F. O., & Masoud, A. S. (2013). Prevalence of pulmonary hypertension in patients with chronic kidney disease on and without dialysis. Egyptian Journal of Chest Diseases and Tuberculosis, 62(4), 761-768. doi: http://dx.doi.org/10.1016/j.ejcdt.2013.09.011

Fabbian F, C. S., Molino C, Pala M, Longhini C, Portaluppi F.. (2010). Pulmonary hypertension in dialysis patients: a crosssectional Italian study. Internal medicine Journal of Nephrology., 11, 463–475.

Grassi G, S. G., Ghiadoni L,. (2011). Sympathetic nerve traffic and asymmetric dimethylarginine in chronic kidney disease. . Clinical Journal of the American Society of Nephrology., 11(6), 2620–2627.

Gurubhagavatula I, P. H. (1997). Pulmonary hypertension in systemic autoimmune disease. Rheumatic Diease Clinics of North America., 23, 365–394.

H. Igarishi, A. K., F. Gejyo, M. Arakawa. (1985). Physiologic approach to dialysis induced hypoxemiaNephron clinical practice, 41, 62–69.

H.W. Farber, A. J. F., D.P. Miller, M.D. McGoon. (2011). correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertensionCongestive Heart Failure journal, . (17), 56-64.

Halpern SC, T. D. (2009). Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. . Chest journal., 136, 37–43.

Hammerstingl, C., Schueler, R., Bors, L., Momcilovic, D., Pabst, S., Nickenig, G., & Skowasch, D. (2012). Diagnostic value of echocardiography in the diagnosis of pulmonary hypertension. Public Library of Science One, 7(6), e38519. doi: 10.1371/journal.pone.0038519

Havlucu, Y., Kursat, S., Ekmekci, C., Celik, P., Serter, S., Bayturan, O., & Dinc, G. (2007). Pulmonary hypertension in patients with chronic renal failure. Respiratory medical journal, 74(5), 503-510. doi: 10.1159/000102953

Humbert, M., Sitbon, O., Chaouat, A., Bertocchi, M., Habib, G., Gressin, V., Yaïci, A., Weitzenblum, E., Cordier, J.F., and Chabot, F. (2010). Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Respiratory Circular. 122, 156-163.

J. Coresh, E. S., L.A. Stevens, J. Manzi, J.W. Kusek, et al., & (2007). Prevalence of chronic kidney disease in the United StatesJournal of America Medical Association(298), 2038–2047.

J. Etemadi, H. Z., R. Firoozi, M.R. Ardalan, M. Toufan, M.M. Shoja, K. Ghabili. (2011). Unexplained pulmonary hypertension in peritoneal dialysis and hemodialysis patientsRevised Portuguese Pneumology.

Jeffery TK, M. N. (2002). Molecular and cellular basis of pulmonary vascular remodeling in pulmonary hypertension. . Prognosis of Cardiovascular Diseases, 45, 173–202.

Kiykim AA, H. M., Ozcan T, Yildiz I, Sari S, Genctoy G. (2010). Pulmonary hypertension in hemodialysis patients without arteriovenous fistula: the effect of dialyzer composition. Renal Failure journal, 32, 1148–1152.

Kolilekas L, G. P., Liasis N, Anagnostopoulos GK, Eleftheriadis I:. (2006). Unusual case of pulmonary hypertension. Respiratory circular, 73, 117–119.

Kosmadakis, G., Aguilera, D., Carceles, O., Da Costa Correia, E., & Boletis, I. (2013). Pulmonary hypertension in dialysis patients. Renal Failure journal, 35(4), 514-520. doi: 10.3109/0886022x.2013.766559

Kosturakis, D., Goldberg, S. J., Allen, H. D., & Loeber, C. (1984). Doppler echocardiographic prediction of pulmonary arterial hypertension in congenital heart disease. The American Journal of Cardiology, 53(8), 1110-1115. doi: http://dx.doi.org/10.1016/0002-9149(84)90646-5

Kuzela DC, H. W., Conger JD, Winter SD, Hammond WS:. (1977). Soft tissue calcification in chronic dialysis patients. . American Journal of Pathology, 86, 403–424.

L. Kumbar, P. A. F., M.A. Rafiq, C. Borawski, J. Chattopadhyay, M.M. Avram. (2007). Pulmonary hypertension in peritoneal dialysis patientsAdvances in Peritoneal. Dialysis., 23, 127–131.

LJ., R. (1997). Primary pulmonary hypertension. New England Journal of Medicine., 336, 111–117.

M.P. Dhakal, M. C. K., M.A. Shelly, T.E. Taley, & (1999). Post-hemodialysis hypoxia occurs in both biocompatible and bioincompatible dialyzersDialysis Transplant journal,, 28, 666–672.

Mallamaci F, T. G., Maas R, Malatino L, Böger R, Zoccali C. . (2004). Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. Journal of American Society of Nephrology., 15, 435–444.

Martin, K. B., Klinger, J. R., & Rounds, S. I. S. (2006). Pulmonary arterial hypertension: New insights and new hope. Respirology, 11(1), 6-17. doi: 10.1111/j.1440-1843.2006.00778.x

Mesa RA, E. E., Dunn WF, Edwards WD. (1998). Human immunodeficiency virus infection and pulmonary hypertension. Mayo Clinic Proceedings journal., 73, 37–45.

Milliner DS, Z. A., Lieberman E, Landing B: . (1990). Soft tissue calcification in pediatric patients with end-stage renal disease. . Kidney International journal, 38, 931–936.

N.M. Aurigemma, N. T. F., M. Gottlieb, R.H. Ingram Jr, J.M. Lazarus, E.G. Lowrie. (1977). Arterial oxygenation during hemodialysisNew England Journal of Medicine (297), 871–873.

Nakhoul, F., Yigla, M., Gilman, R., Reisner, S. A., & Abassi, Z. (2005). The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. Nephrology Dialysis Transplant, 20(8), 1686-1692. doi: 10.1093/ndt/gfh840

ND:, V. (2001). Effect of chronic renal failure on nitric oxide metabolism. American Journal of Kidney Disease, 38, S74–S79.

Niederle, P., Starek, A., Jezek, V., & Hes, I. (1988). Doppler echocardiography in the diagnosis of pulmonary hypertension. Cor et Vasa journal, 30(4), 272-280.

Okura H, T. Y. (1994). High output failure as a cause of pulmonary hypertension. . Internal Medicine journal, 33, 363–365.

Palevsky HI, F. A. (1990). Chronic cor pulmonale. Etiology and management. Journal of America Medical Association, 263, 2347–2353.

Perez-Penate G, C. N. P., Ponce Gonzalez M, Gorriz Gomez E, Pulido Duque J, Garcia Quintana A, Julia Serda G:. (2005). Long-term inhaled nitric oxide plus dipyridamole for pulmonary arterial hypertension. . Respiration journal, 72, 419–422.

Ressl J, U. D., Widimský J, Ostádal B, Pelouch V, Procházka J. . (1974). Reversibility of pulmonary hypertension and right ventricular hypertrophy induced by intermittent high altitude hypoxia in rats. Respiration journal., 31, 38–46.

S. Marangoni, A. Q., A. Dotti, S. Scalvini, M. Volterrani, M. Schena, et al. (1988). Noninvasive assessment of pulmonary hypertension: a simultaneous echo-Doppler hemodynamic studyCardiology journal. (75), 401-408.

S. Pabst, C. H., F. Hundt, T. Gerhardt, C. Grohe, G. Nickenig, R. Woitas, D. Skowasch, . (2015). Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. Results of the PEPPER-study. PLoS One 7(4),, 16(9), 578-582.

Sakaguchi Y, S. T., Kawabata H, et al. (2011). High prevalence of obstructive sleep apnea and its association with renal function among nondialysis chronic kidney disease patients in Japan: a cross-sectional study. . Clinical Journal of American Society of Nephrology., 6, 995–1000.

Sakao S, T. K., Voelkel NF. (2010). Reversible or irreversible remodeling in pulmonary arterial hypertension. American Journal of Respiratory Cell and Molecular Biology, 43, 629–634.

Sica AL, G. H., Ruggiero DA, Scharf SM. (2000). Chronicintermittent hypoxia: a model of sympathetic activation in the rat. Respiratory Physiology journal., 121, 173–184.

Soki, A.J. Were, E.N. Ogola, G.M. Nyale, M.M. Murage. (2017). An echocardiographic evaluation of pulmonary pressures in hemodialysis patients at Kenyatta National Hospital, Nairobi, Kenya.East African Medical Journal.

Soroush-Yari A, B. S., Hoo GW, Santiago SM:. (2005). Pulmonary hypertension in men with thyrotoxicosis. Respiration journal, 72, 90–94.

Taleb, M., Khuder, S., Tinkel, J., & Khouri, S. J. (2013). The diagnostic accuracy of Doppler echocardiography in assessment of pulmonary artery systolic pressure: a meta-analysis. Echocardiography, 30(3), 258-265. doi: 10.1111/echo.12061

Tiengo, A., Fadini, G., & Avogaro, A. (2008). The metabolic syndrome, diabetes and lung dysfunction. Diabetes & metabolism, 34(5), 447-454.

Trenton D. Nauser, M. D., and Steven W. Stites, M.D. . (2001).Pulmonary Hypertension in chronic kidney disease.American Family Physician, 63(9), 1789-1799.

Tripepi G, M. R. F., Sijbrands E, et al. . (2011). Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in ESRD patients. Clinical Journal of American Society of Nephrology., 6, 1714–1721.

Unal, A., Tasdemir, K., Oymak, S., Duran, M., Kocyigit, I., Oguz, F., . . . Oymak, O. (2010). The long-term effects of arteriovenous fistula creation on the development of pulmonary

hypertension in hemodialysis patients. Hemodialysis International journal, 14(4), 398-402. doi: 10.1111/j.1542-4758.2010.00478.x

Ward JP, M. I. (2009). Mechanisms of hypoxic pulmonary vasoconstriction and their roles in pulmonary hypertension: new findings for an old problem. Curr ent Opinion in Pharmacology, 9, 287–296.

Wedgwood, S., Devol, J. M., Grobe, A., Benavidez, E., Azakie, A., Fineman, J. R., & Black, S. M. (2007). Fibroblast growth factor-2 expression is altered in lambs with increased pulmonary blood flow and pulmonary hypertension. Pediatric Respiratory medicine journal, 61(1), 32-36. doi: 10.1203/01.pdr.0000250013.77008.28

Yigla M, A. Z., Reisner SA, Nakhoul F. (2006). Pulmonary hypertension in hemodialysis patients: an unrecognized threat. Seminars in Dialysis, 19, 353–357.

Yigla, M., Nakhoul, F., Sabag, A., Tov, N., Gorevich, B., Abassi, Z., & Reisner, S. A. (2003). Pulmonary hypertension in patients with end-stage renal disease. Chest journal, 123(5), 1577-1582.

Zoccali C, M. F., Tripepi G. . (2002). Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. Journal of American Society of Nephrology., 3, 729–733.

APPENDIX I: Data collection form

Demographic data

1. Patient number

2. Study ID:.....

3. DOB:……..Gender: Male..... Female.....

4. Residence ..... 5. Occupation.....

6. Do you take alcohol? Yes..... No..... 7. Do you smoke? Yes.....No.....

8. Which fuel do you use for cooking?Charcoal.....firewood.....

Electricity.....solar.....gas.....

Clinical features

1. Vitals: BP..... PR..... RR..... SPO2..... WT.....

:RBS.....

2. Lab Results:

I. CBC:

HB	
HCT	

II. U/E/C:

BUN	
Cr	
K	

III. Phosphate, Calcium

Po4	
Ca	

IV.Urinalysis

Parameter	**Value**
Protein	
Creatinine	

V. Liver function tests

Parameter	**Value**
Albumin	
ALT	
AST	

- Are you undergoing Dialysis : Yes..... No.....

- ❑ If yes in above: Which modality.....

:How many times a week ..... Duration since onset.....

- ❑ Which Venous access are you using for dialysis a) AVF.....

b)subclavian/jugular catheter.....

c) tunnel /perm. catheter.....

- ❑ Are you a known hypertensive: Yes.....No .....
- ❑ If yes in above are you on antihypertensives? Yes..... No.....
- ❑ Are you a known diabetic: Yes..... No.....
- ❑ If yes in above are you on hypoglycemics? Orals: Yes..... No.....

Insulin: Yes.....No.....

- ❑ Are you a known asthmatic? Yes..... No.....
- ❑ Have you been diagnosed with chronic lung disease? Yes..... No.....
- ❑ HIV Status: Negative:..... Positive:..... Do not Know:..... Declined test:.....

Echocardiography Findings:

Part A.

1. ECHO Number:.....

2. Previous ECHO Report:.....

.....

.....

3. Brief clinical history.....

.....

Part B.

Situs:

Venous Return:

Great Arteries:

Valves:

Chambers:

Septa:

Pericardium:

LV Systolic Function:

Wall Motion:.....

.....

LV Diastolic Function:

PART C.

M-Mode Measurements:

RV:	**LVIDD:**	**LVIDS:**	**LA:**
IVS:	**LVPW:**	**AO:**	**FS:**
HR:	**SV:**	**ESV:**	**EDV:**

Conclusion:

Additional Comments:

ECHO Reported by:..... Date:.....

APPENDIX II: Consent form (English version)

I .....,from..... Hospital No..... consent to the participation of this study to determine the prevalence of pulmonary hypertension in chronic kidney disease, a study being conducted by Dr. Seth Nyambane Mayaka a post-graduate student in school of medicine, Moi University.

Pulmonary hypertension is a condition affecting the function of the lung leading to poor oxygenation of blood and eventually can cause heart failure and death if not diagnosed early and managed appropriately. A number of factors lead to the development of this condition and it has been shown to be prevalent among patients with chronic kidney disease. Its prevalence in chronic kidney disease has been shown to be associated with increased morbidity and mortality and a worse outcome in advanced stages of chronic kidney disease. The extent of pulmonary hypertension among patients with chronic kidney disease has not been established in Kenya. Additionally, there is need to understand its impact on the progression of kidney failure so as to guide clinicians on prompt intervention because well established pulmonary hypertension is irreversible.

Estimation of pulmonary pressure will be done using Doppler echocardiography which is a non-invasive procedure. A probe will be placed on the patients' chest to estimate the pulmonary pressure. The results will come out in a print out which will be explained to the patient.

Blood samples will be taken from the superficial veins for analysis to help determine the associated correlates. Urine samples will also be taken for analysis to correlate the clinical findings. Other samples will be taken as deemed necessary by the attending clinician.

I have been informed that my follow up and treatment is independent of my consent to participation. I may withdrawfrom this study at my will.

I have also been assured that the investigations pose no risk to my health and that details retrieved from my medical records concerning my diagnosis and treatment will remain confidential.

Participant's Sign..... Researcher's Sign.....

Date..... Date.....

APPENDIX III: Consent form (Kiswahili version)

Mimi.....kutoka..... Nambari ya hospitali.....

nimeridhia kushiriki katika utafiti ambao unatathmini kuwepo kwa presha ya juu ya damu kwenye mapafu kwa wagonjwa wenye ugonjwa wa figo, utafiti ambao unafanywa na Daktari Seth Nyambane Mayaka mwanafunzi katika shule ya matibabu chuo kikuu cha Moi.

Shinikizo la damu kwenye mapafu ni ugonjwa unaodhuru kazi ya mapafu na mwishowe husababisha shida ya ubadilishanaji wa gesi haswa oxygen na inaweza sababisha shida ya moyo na hata kifo endapo hautavumbuliwa mapema na kutibiwa ipasavyo.

Kunazo chanzo nyingi zinazochangia ugonjwa huu na visa vingi vimeripotiwa kwa wagonjwa ambao wana ugonjwa wa figo. Visa hivi vinachangia uwezekano wa kuwa mgonjwa zaidi na hata kusababisha vifo na matokeo mabaya kwa wagonjwa ambao figo zao zimedhoofika zaidi.

Zaidi ya hayo kuna haja ya kuelewa madhara ya shinikizo la damu kwenye mapafu kwa figo ili kusaidia wauguzi kuweka mikakati ya matibabu kwa sababu endapo shinikizo la damu kwenye mapafu limekita basi ni vigumu kutibu madhara yake.

Kukadhiria shinikizo la damu kwenye mapafu itafanywa kutumia kifaa cha Doppler ultrasound ambayo ni utaratibu zisizo vamizi. Kidude kitawekwa juu ya kifua cha wagonjwa kukisia shinikizo kwa mapafu. Matokeo yatachapishwa kwa karatasi na mgonjwa kuelezwa.

Sampuli za damu zitachukuliwa kutoka mishipa ya juu juu kwa ajili ya uchambuzi ili kusaidia kuambatisha matokeo ya kliniki. Sampuli zingine zitachukuliwa endapo muuguzi ataona umuhimu.

Nimefahamishwa kwamba matibabu yangu ni huru ya idhini yangu kushiriki utafiti huu. Naweza kuondoka kutoka utafiti huu kwa hiari yangu.

Sampuli ya mkojo zitachukuliwa pia kwa ajili ya uchambuzi kuambatisha matokeo ya kliniki. Sampuli nyingine zitachukuliwa kama aliona muhimu na daktari mhudhuru.
Nimehakikishiwa kwamba uchunguzi huu hausababishi hatari kwa afya yangu na kwamba maelezo ya Rudishwa kutoka kumbukumbu zangu za kiafya kuhusu uchunguzi wangu na matibabu itabaki siri.

Sahihi ya mshiriki.....sahihi ya mtafiti.....

Tarehe.....Tarehe.....

APPENDIX IV: PROCEDURE FOR MEASURING BLOOD PRESSURE

Blood pressure was taken using an Omron M2 compact upper arm blood pressure monitor (**Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015**).

The patient was placed in a quiet place, in a relaxed sitting position with no tight fitting clothing on the upper arm, or any thick clothing such as a sweater.

The patient sat upright with the back straight and placed the arm on the table so that the cuff was on the same level as the heart. The cuff was wrapped on the right arm such that the bottom of the cuff was at least 1cm above the elbow. It was then fastened snugly. The start button on the machine was then pressed and automatically the cuff beganto inflate and the machine took a reading. The blood pressure results as well as a heart rate reading were then displayed on the screen.

If an error occurred, the cuff was deflated and the process repeated. High blood pressure readings were confirmed manually using a mercury sphygmomanometer.

The blood pressure machines were calibrated every week.

APPENDIX V: PROCEDURE FOR DRAWING BLOOD

The procedure was explained to the patient and verbal consent sought.

Universal precautions were observed.

A tourniquet was applied at a distal site about 5cm proximal to the selected site of venipuncture. The patient was asked to make a fist without pumping the hand. The phlebotomist put on a pair of clean gloves. The selected site was cleaned thoroughly with methylated spirit or povidone Iodine starting with the center and working outward. It was then allowed to dry.

The patient's arm was grasped firmly using the thumb to keep the skin taut and to anchor the vein. A sterile Vacutainer® system (**Becton, Dickinson and Company, 1 Becton Drive, Franklin Lakes, NJ USA 07417**) was opened and the blood collection needle inserted gently into the lumen of the vein at an angle of 15- 30^{o}, then the other end was attached to a Vacutainer® blood collection bottle. Blood flowed freely into the bottle due to negative pressure. 2ml of blood for serum creatinine, 2mls for uric acid determination was collected in a plain bottle and another 2ml was collected in a S.S.T-bottle and used for determination of the lipid profile.

After adequate blood had been collected, the tourniquet was released then the Vacutainer® needle was removed gently and an alcohol impregnated swab was applied at the site under pressure. Pressure was applied for a whole minute then the site was reassessed for continued bleeding. The area was dressed with a dry gauze and tape.

APPENDIX VI: PROCEDURE FOR TESTING BLOOD GLUCOSE

Instrument used: HemoCue Glucose 201+

Principles:

The HemoCue Glucose 201+ is a system for the determination of the total amount of glucose in whole blood. Capillary, venous or arterial blood may be used. It utilizes a modified glucose

dehydrogenase method. A chromogen compound is added to the reagents with saponin used for haemolysing the erythrocytes. The absorbance is measured at two wavelengths (660 and 840nm) to compensate for turbidity.

Testing Procedure: Procedure was explained to the subject and consent obtained. . A drop of blood from the blood collected from the vein for other tests, was placed at the tip of the micro cuvette allowing it to fill in a continuous process making sure that there were no air bubbles. Excess blood on the outside of the micro cuvette tip was wiped off without drawing blood out of the cuvette. If there were air bubbles, the test was repeated with a new sample of blood. The filled micro cuvettewas placed in the cuvette holder within 40 seconds of filling the cuvette and the cuvette holder pushed to its measuring position. Test results were automatically displayed in 40-240 seconds.

Quality Control

The HemoCue Glucose 201+ analyser has an internal electronic „SELFTEST□. Every time the analyser is turned on, it will automatically verify the performance of the optronic unit of the analyser. This test was performed every second hour if the analyser was left turned on.

Measuring range:

0-30 mmol/L (0-540mg/dL). Results above 30mmol/L (540mg/dL) will be displayed as HHH.

IVD Medical Device Directive:

The HemoCue Glucose 201+ complies with the IVD Medical Device Directive 98/79/EC and carries the CE mark. 61

APPENDIX VII: CKD Epi calculator for GFR estimation

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was developed in an effort to create a formula more precise than the MDRD formula, especially when actual GFR is > 60 mL/min per 1.73 m^2. It is as a result of pooled data from multiple studies to develop and validate this new equation. The CKD-EPI equation performs better than the MDRD (Modification of Diet in Renal Disease Study) equation, especially at higher GFR, with less bias and greater accuracy.

The CKD-EPI equation, expressed as a single equation, is:

$GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

APPENDIX VIII: Doppler Echocardiography technique

1. Doppler Echocardiography

   - ❖ Machine – Phillips Xmatrix (Made in USA)

- Probe- Adult S5-1

   - ❖ Approach- Triage

-The procedure was explained to the patients then the upper body was exposed and covered with a gown. The patient was then positioned in the lateral position and the gel was applied on theprobe. The probe was then positioned in appropriate windows to give the full echocardiography details. The windows used included:

I. PLAX (Long parasternal axis of the RV Inflow)

II. Apical 4 window

III. SAX (Short Axis LV/AOV- RV Outflow tract)

IV. Apical 2

V. Apical 3

VI. Subcostal- IVC

A tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler echocardiography probe. Systolic right ventricular (or pulmonary artery) pressure was calculated using the modified Bernoulli equation: PAP = 4 × (tricuspid

systolic jet) 2 + 10 mmHg (estimated right atrial pressure). . This instrument sends sound waves into the chest and picks up the echoes as they reflect off different parts of the heart. The echoes are sent to a video monitor that records pictures of your heart for later viewing and evaluation. The room was darkened to help the technician see the pictures on the monitor.

At times the patients were asked to hold very still, breathe in and out very slowly, hold their breath, or lie on their left side. The transducer was momentarily moved to different areas of the patients'chest that provided specific views of the heart.

The test usually took 30 to 60 minutes. When the test was over, the gel was wiped off

Scanning and reportingwas done within 4hrs after dialysis. Two trained, dedicated and qualified technicians performed the echocardiography as per standard protocol of the Moi Teaching and Referral Hospital.

APPENDIX XI: CLASSIFICATION OF PULMONARY HYPERTENSION

Table 1: UPDATED CLASSIFICATION OF PULMONARY HYPERTENSION(DANA POINT 2008)

1. Pulmonary arterial hypertension 1.1 Idiopathic PAH 1.2 Heritable PAH 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown 1.3 Drug and toxin induced 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis1". Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease 2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold.**

BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

APPENDIX X II: MTRH/ IREC APPROVAL FORMS

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4
Fax: 61749
Email: director@mtrh.or.ke

P. O. Box 3
ELDORET

Ref: ELD/MTRH/R.6/VOL.II/2008

23rd September, 2014

Dr. Seth Mayaka,
Moi University,
School of Medicine,
P.O. Box 4606-00200,
ELDORET-KENYA.

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:

"Prevalence of Pulmonary Hypertension in Adult Patients with Chronic Kidney Disease at Moi Teaching and Referral Hospital."

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR.JOHN KIBOSIA

DIRECTOR
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Chief Nurse
- HOD,HRISM

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
23 SEP 2014
APPROVED
P.O. Box 4606-30100 ELDORET

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

Reference: IREC/2014/194
Approval Number: 0001280

23rd September, 2014

Dr. Seth Mayaka,
Moi University,
School of Medicine,
P.O. Box 4606-00200,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
23 SEP 2014
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Mayaka,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Prevalence of Pulmonary Hypertension in Adult Patients with Chronic Kidney Disease at Moi Teaching and Referral Hospital."

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1280*** on 23rd September, 2014. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 22nd September, 2015. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

For

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc Director - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD