THE RELEVANCE OF PERFORMING 24-HOUR AMBULATORY BLOOD PRESSURE AND PULSE WAVE ANALYSIS IN KIDNEY TRANSPLANT RECIPIENTS.

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TABLE OF CONTENTS

ABSTRACT

Hypertension guidelines recommend out of office blood pressure (BP) measurement especially 24-hour ambulatory measurement (ABPM), to diagnose and manage hypertension but this is not routinely performed in kidney transplant units.

This study was to determine if 24-hour ABPM, compared with office BP in kidney transplant recipients, would be more informative regarding BP management, and if pulse wave analysis (PWA) would assist in risk stratification.

This study included patients older than 18 years, with working graft kidney for >12 months, and without problems affecting BP measurement and interpretation. After performing office BP measurements, a 24-hour ABPM with additional capability of calculating pulse wave velocity (PWV), augmentation index and central BP was undertaken. Patients were assessed for controlled hypertension, uncontrolled hypertension, masked hypertension, nocturnal hypertension, white coat hypertension, and dipping BP status. Data were analysed using standard statistical tests.

Of 30 patients, 15 were Black Africans and 15 were of Mixed Ancestry with a mean age of 48.9 years. Seventeen patients were males and 36.7% had controlled hypertension, 30% uncontrolled hypertension, 6.7% white coat hypertension and 33.3% masked hypertension, of whom 70% had isolated nocturnal hypertension. 70% had a non-dipping, 26.7% a reverse dipping and only 3.3% had a normal dipping BP pattern. The mean difference between brachial systolic BP and central systolic BP was 10.4 mmHg, whereas PWV and augmentation index were similar to healthy populations.

CONCLUSION: In kidney transplant recipients, 24-hour ABPM was superior to office BP in defining hypertensive status that qualified for modification of therapy but PWA did not contribute to risk assessment.

Key words: Hypertension, kidney transplant recipients, blood pressure measurement, pulse wave analysis.

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TABLE OF TABLES & FIGURES

TABLES

FIGURES

ABBREVIATIONS

ABPM- ambulatory blood pressure monitoring

ACE inhibitor- angiotensin converting enzyme inhibitor

AI- augmentation index

ARB- angiotensin receptor blocker

AV fistula- arteriovenous fistula

BMI- body mass index

BP- blood pressure

CKD- chronic kidney disease

eGFR- estimated glomerular filtration rate

KDIGO- The Kidney disease: Improving global outcome

PWA- Pulse wave analysis

PWV – Pulse wave velocity

CHAPTER 1

MANUSCRIPT

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INTRODUCTION

Hypertension is a common problem in renal transplant recipients and is considered one of the major risk factors for the development of cardiovascular (CV) diseases and declining kidney function (1). CV disease is the most important cause of mortality in renal transplant recipients accounting for 40% of all deaths (2).

Traditionally blood pressure (BP) is measured in the office to diagnose and manage hypertension in the transplant clinic. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the treatment of hypertension in chronic kidney disease (CKD) suggest that adult kidney transplant recipients whose office blood pressure is consistently >130 mmHg systolic or >80 mmHg diastolic be treated to maintain a BP that is consistently <130 mmHg systolic and <80 mmHg diastolic, irrespective of urine albumin excretion (3). However, no recommendation was made regarding the use of out of office BP measurement.

In 2020, most major international guidelines recommended out of office BP measurements, especially 24-hour ambulatory blood pressure measurements (ABPM), to diagnose and manage hypertension (4,5). The National Institute of Health and Care Excellence guidelines have emphasized the superiority of out of office over office BP measurements (6). However, despite hypertension being common among renal transplant recipients, diagnosis and management is generally assessed by office BP.

Twenty four-hour ABPM is superior to office BP in predicting hypertension-mediated organ damage, has the advantage of detecting white coat and masked hypertension, and provides important information on nocturnal blood pressure and dipping status. Non-dipping pattern is associated with more severe hypertension-mediated organ damage and increased CV risk, not only in the presence of hypertension but also in normotensive individuals (7).

In health, the central BP is lower than the brachial BP due to amplification of the pulse wave as it progresses down the arterial tree. Patients with CKD develop vascular stiffening related to calcification, amongst other factors (8,9,10). This results in progressive stiffening and loss of elasticity of the central arteries, and the pulse wave velocity (PWV) of the reflection wave is increased resulting in augmentation of central systolic BP and increased pulse pressure (11). The Mobile-O-Graph (Industrielle Entwicklung Medizintechnik and Vertriebsgesellschaft company located in Cockkerillstr 69, 5222 Stolberg, Germany) is a certified 24-hour ambulatory BP monitor. It also calculates central BP, augmentation index and PWV by a dedicated algorithm (11,12) and may provide additional information beyond BP to identify patients at risk of CV diseases and renal allograft loss. Increased PWV is associated with death and progression of CKD and provides additional risk stratification (13). In kidney transplant recipients, PWV predicted mortality (14).

There are few studies exploring the use of 24-hour BP monitoring and pulse wave analysis (PWA) in kidney transplant recipients. With this in mind, we aimed to conduct a study in kidney transplant recipients to determine if the use of 24-hour ambulatory BP monitoring compared to the office BP would provide clinically relevant information in regard to management of BP and if additional information provided by pulse wave analysis (PWA) would assist in risk stratification.

METHODS

The study was approved by the Health Science Human Research Ethic Committee of the University of Cape Town (reference number: 294/2019). This was a prospective observational study conducted in the kidney transplant clinic at Groote Schuur Hospital between June 2019 to May 2020.

The inclusion criteria were kidney transplant recipients older than 18 years with a stable estimated GFR attending the outpatient clinic, and a successful kidney transplant performed more than 12 months ago. Written informed consent was obtained in all patients.

Patients were excluded if they were acutely unwell with suspected sepsis, acute rejection or any acute illness affecting BP levels. In addition, there was inability to apply the cuff to the brachial artery due to obesity or bilateral arterio-venous (AV) fistulas.

A convenience sample of 30 kidney transplant recipients was planned for the study as there was only one ABPM machine available to use on each clinic day over a limited study period.

The following patient characteristics were recorded: age, sex, ethnicity, cause of CKD, comorbidities, date of transplantation, office BP, body mass index (BMI), waist circumference, kidney function and CKD stage, and chronic medication.

BLOOD PRESSURE MEASUREMENT

After informed consent, office BP was performed unobserved in the clinic after 5 minutes rest in a quiet environment using validated automated device (OMRON HBP-1300 manufactured by Sole: Omron Corporation, Japan) in accordance with South African Hypertension Practice guidelines (15). The mean of 3 stable readings was used to calculate the office BP.

The choice of arm was dependent on the presence of prior vascular surgery and patient preference for application of the ABPM. Both ambulatory and office BP had to be performed in the same arm to avoid inter arm differences in BP. The 24-hour ABPM was performed using Mobil-O-Graph monitor that was able to calculate PWV, central BP and augmentation index through a dedicated software algorithm. The day time period was defined as 6am-10pm and night time from 10pm-6am.

BP was measured every 20 minutes during the day and every 30 minutes at night. In order to be valid, >70% of readings had to be recorded. The ABPM was applied immediately after the office BP measurements.

DEFINITIONS

Uncontrolled hypertension was defined as mean office BP ≥140/90 mmHg and 24-hour ambulatory BP ≥135/85 mmHg during the day and/ or ≥120/70 mmHg at night, and controlled hypertension or normotension as office BP<140/90 mmHg and mean daytime ambulatory BP<135/85 mmHg and night time<120/70 mmHg. White coat hypertension was defined as mean office BP ≥140/90 mmHg, but daytime ABPM<135/85 mmHg, and masked hypertension as mean office BP<140/90 mmHg, but daytime ambulatory BP ≥135/85 mmHg and/or night time BP≥120/70 mmHg. Dipping was defined as >10% drop in mean BP during the night compared to BP during the day, non-dipping as 0-10% drop, and reverse dipper as a rise in BP.

Augmentation index, PWV and central BP were determined by a dedicated algorithm of the Mobile - O-Graph.

DATA MANAGEMENT AND ANALYSIS

The data obtained from the subjects were entered into an Excel spreadsheet and analysed. Mean, median and standard deviation were calculated using standard formulae using Excel.

RESULTS

A total of 34 patients entered the study, but four patients were excluded because they did not complete the ABPM. Of the remaining 30 patients, 15 were Black Africans and 15 of Mixed Ancestry with mean age of 48.9 years. There were 17 males (56.7%), and a median renal graft age of 5 years (range 1 to 18 years). (Table 1) Twenty-five renal grafts (83.3%) were from cadaver donors. All the patients were on immunosuppressive drugs, usually a combination of calcineurin inhibitors, antimetabolites and low dose prednisone 5mg daily. The causes of end stage renal disease were chronic glomerular disease in 11 patients (36.7%), hypertension in 10 patients (33.3%), human immunodeficiency virus associated nephropathy in 4 patients (13.3%), autosomal dominant polycystic kidney disease in 4 patients (13.3%) and analgesic nephropathy in 1 patient (3.3%). There were 23 patients treated for hypertension and 8 patients had diabetes mellitus at the time of the

study. Out of the total study population, five patients (16.7%) had stage 1 CKD, six patients (20%) had stage 2 CKD, thirteen (43.3%) had stage 3 CKD, four (13.3%) had stage 4 CKD, and two (6.7%) had stage 5 CKD. The mean body mass index was 27.4m^2/kg, and the mean waist circumference in women 96 cm and in men 96.7 cm.

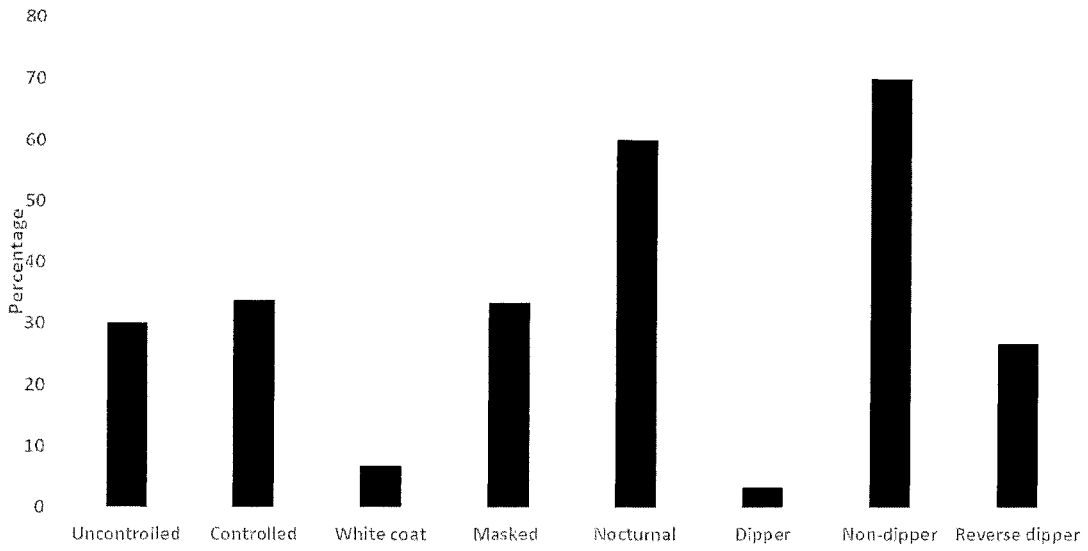
Table 1: Patient characteristics

PARAMETER	**N = 30**
Mean age	48.9 years
Males	17 (56.7%)
Ethnicity:	
Blacks	15 (50%)
Mixed ancestry	15 (50%)
Diabetes mellitus	8 (26.7%)
Mean kidney graft age	5 years
Mean serum creatinine	145.6 mmol/l
Mean eGFR	54.5 ml/min
Antihypertensive treatment	
Calcium channel blockers	56.7%
ACE inhibitor/ARB	40%
Diuretics	20%
Beta blockers	36.7%
Alpha-1-receptor blocker	33.3%
Other	6.7%
Mean BMI	27.4 kg/m^2
Mean waist circumference	
Male	96.7 cm
Female	96 cm
CKD STAGE	
Stage 1	16.7%
Stage 2	20%
Stage 3	43.3%
Stage 4	13.3%
Stage 5	6.7%
Deceased donor kidney	25 (83.3%)
BP measurement	
Mean office BP	134.2/82 mmHg
Mean overall 24-hour ABPM	129.9/83.9 mmHg
Mean daytime 24-hour ABPM	131/85.2 mmHg
Mean night-time 24-hour ABPM	126.8/80.3 mmHg

Legend: ARB – angiotensin receptor blocker, ABPM = ambulatory blood pressure monitoring

There was mean office BP of 134.2/82 mmHg, mean day time 24-hour ambulatory BP of 131/85.2 mmHg and mean night time 24-hour ambulatory BP of 126.8/80.3 mmHg. In figure 1, patients labelled as uncontrolled, had elevated office BP, day time BP and night time BP. There were nine of them (30%). Out of patients with uncontrolled hypertension, 77.8% of patients were on antihypertensive medication while 22.2% were newly diagnosed, giving an overall prevalence of hypertension in our study of 90%, based on ABPM. In figure 1, patients labelled as controlled, had normal office BP, day time BP and night time BP. There were eleven of them (36.7%). Out of the 11 patients with controlled BP, 9 were on antihypertensive treatment while 2 were not on treatment. Two patients (6.7%) with white coat hypertension also showed isolated nocturnal hypertension. In the whole study, we identified ten patients (33.3%) with masked hypertension and of these ten patients, seven patients (70%) had isolated nocturnal hypertension. Overall, there were eighteen patients (60%) with nocturnal hypertension in our population. There were 21 non-dippers (70%), 8 reverse dippers (26.7%) and 1 dipper (3.3%).

Figure 1. Classification of BP by office and ambulatory blood pressure measurement



The mean difference between brachial systolic BP and central systolic BP was 10.4 mmHg. Table 2 and 3 show the results of PWV and augmentation index values respectively, grouped according to ages, and compared to the normal reference values for the healthy population.

Table 2: PWV values from renal transplant recipients and PWV values from normal healthy population grouped according to ages (no difference between groups) (16).

AGE IN YEARS	**PWV - Subjects results in m/s**			**PWV – Normal value for population in m/s**		
Age group	Mean	Min	Max	Mean	Min	Max
<30 years	5.6	5.3	5.9	6.2	4.7	7.6
30-39 years	4.7	5.3	6.7	6.5	3.8	9.2
40-49 years	6.7	6.2	7.3	7.2	4.6	9.8
50-59 years	7.8	7.2	9.1	8.3	4.5	12.1
60-69 years	9.2	8.1	9.9	10.3	5.5	15

Legend: PWV – pulse wave velocity

Table 3: Augmentation index values from kidney transplant recipients and augmentation index values from normal healthy population grouped according to ages (no difference between groups) (17).

AGE (years)	Subjects AI (mean±sd)	Normal AI (mean±sd)
<39 years	19.17±22.69	23.40±8.4
40-49 years	22.08±21.36	28.9±10.3
50-59 years	23.40±32.8	29.7±9.1
>60 years	34.10±5.45	34.1±9.0

Legend: AI= augmentation index

DISCUSSION

The principal findings of our study were that in kidney transplant recipients 24-hour ABPM was superior to office BP in defining hypertensive status and demonstrated a potential for modification of antihypertensive therapy in the vast majority. Office BP correctly identified controlled

hypertension in only 36.7% of participants, but only one of these patients had a normal dipping status. Non-dipping and reverse dipping are commonly reported in patients with CKD and are associated with worse outcomes. In the Hygia study, nocturnal dosing of at least one antihypertensive drug significantly improved CV outcomes possibly by optimising night time BP control (18). Furthermore, reverse dipping may also be linked to sleep apnoea, which is common in CKD (19), and should prompt consideration for performing a sleep study.

Thirty percent of patients had uncontrolled hypertension, (of which 6.7% were newly diagnosed), and qualified for optimisation of BP treatment or introduction of antihypertensive drugs. One third of participants had masked hypertension which would not have been identified by routine BP measurements. Of these patients, 70% had isolated nocturnal hypertension. Masked hypertension is associated with poorer CV outcomes (20) and this finding should prompt intensification of antihypertensive treatment especially at night in those with isolated masked nocturnal hypertension. The white coat effect was uncommon, being present in only 6.7%, but both of these participants also had isolated nocturnal masked hypertension. The white coat effect may have been mitigated by the use of automated unobserved BP measurement (21).

The prevalence of hypertension in our study based on ABPM was 90%, similar to that reported by Ravichandran et al. at 91.9% (22). However, in the literature there are significant differences in the prevalence of white coat and masked hypertension, and dipping status. For example, the prevalence of white coat hypertension ranged from 3% to 24.1% (23,24,25), masked hypertension from 14% to 58% (23,24,25) and isolated nocturnal hypertension from 11% to 33% (23,25,26). Similarly, in regard to dipping status, normal dipping ranged from 5.4% to 26.7% of patients (22,26), reverse dipping in 20% of patients (26) and non-dipping BP from 53% to 94.6% of patients (22,24,26). The difference in these studies is probably related to the method of office BP measurement (AOBP unobserved versus traditional measurement), the severity of CKD, and ethnic mix of patients. Our study was conducted in exclusively black Africans or mixed ancestry patients where non-dipping rates are reported to be

higher (27). However, the consensus of all the studies is that 24-hour ABPM is an essential tool in fully evaluating the BP profile of kidney transplant recipients.

In our study the PWA did not contribute significantly to the assessment. The mean difference between the brachial systolic BP and central systolic BP was 10.4 mmHg, which is within the normal range of 10-20 mmHg (28). Furthermore, PWV and augmentation indices in our patients were similar to those obtained from normal healthy populations of same age group (16). No patient had a PWV>10 m/s which is linked to adverse cardiovascular outcome (29). In addition, augmentation index values obtained in our study population were comparable to those obtained from normal healthy populations of same age. No patient had an augmentation index >40%, which is diagnostic of large artery stiffness in adult subjects (17). The normal PWV and augmentation index in our renal transplant recipients may be related to reported improvement of vascular remodelling observed in CKD within 12 months of kidney transplantation (30). Improvement of aortic wall elastic properties after renal transplantation is a continuous and prolonged process (31).

The limitations of the study are the small sample size, and the possibility of referral bias in selecting patients. The strength of our study lies in complete data collection and performing both office BP and 24-hour ambulatory BP on the same day and same arm in all patients.

CONCLUSION

Twenty four-hour ABPM was superior to office BP in identifying all forms of hypertension, especially masked uncontrolled nocturnal hypertension. This study suggests that 24-hour ABPM, in addition to office BP, should become the standard of care for the diagnosis and management of hypertension in kidney transplant recipients. The future study on this topic is required but large sample size and presence of control group will be of value.

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APPENDIX:

DATA COLLECTING SHEET

NAME	GSH	DOB
GENDER	ETHNICITY	WEIGHT
HEIGHT	WAIST CIRCUMFERENCE	BMI
CAUSE OF CKD	CURRENT GFR	CKD STAGE
CURRENT CREATININE	LVH	CURRENT MEDICATIONS
DOT	3 RESTING BP ON NON-FISTULA ARMS: 1.	
		2.
		3.
TYPE OF DONOR	COMMORBIDITIES	

INFORMED CONSENT

RESEARCH TITTLE

RELEVANCE OF MEASURING 24HOUR AMBULATORY BLOOD PRESSURE, PULSE WAVE VELOCITY AND CENTRAL BLOOD PRESSURE IN KIDNEY TRANSPLANT RECIPIENTS.

RESEARCHERS

1. **Luvuyo Mzingeli** **Principal investigator**
2. **Professor Rayner** **Supervisor**

INTRODUCTION

We are welcoming you as a participant in this study. This document will help inform you about the project before you consent to participate in this study. Feel

free to ask any questions after reading this document or at any time during the study.

Participation is voluntary. If you do not agree to participate it will not affect your regular medical care.

WHY IS THE STUDY BEING CONDUCTED?

Studies have shown that kidney transplant recipients are at risk of diseases that affect the heart and its blood vessels which negatively affect their quality of life and life expectancy. Control of blood pressure (BP) in kidney transplant recipients is critical for the long-term survival of the kidney and prevention of cardiovascular diseases, and routine office blood pressure may not be ideal in this assessment. Studies have observed a link between kidney disease and stiffening of blood vessels and its impact on cardiovascular diseases. With a new generation 24-hour blood pressure monitor, we are able to measure blood pressure over the entire day and night as well as calculating stiffness of the arteries.

WHY ARE YOU THE RIGHT CANDIDATE FOR THE STUDY?

Since you have had kidney disease and kidney transplant, blood pressure control is very important and your blood vessels are at risk of being stiff.

DURATION OF THE STUDY

The study will take approximately 8 months and you will be among one of the 30 participants in the study.

PROCEDURES TO BE PERFORMED

1. You will be interviewed by the researcher to ask you about your age, ethnicity, date of transplantation, chronic illness and chronic medication.

2. Physical examination: record your sex, office blood pressure, height, weight, (body mass index) BMI and Waist circumference.

3. Investigations: ECG- which is done by attaching stickers on the chest wall to check the effect of stiffening of blood vessels on the heart and its enlargement.

4. Mobil-O-Graph (a harmless machine) that records your blood pressure, pulse wave velocity and central blood pressure over 24 hours. It will be attached to your body while you are still in the clinic and it will not be removed until the following day when you come to the clinic for its removal. While attached to you, it will measure your blood pressure every 20 minutes in the day and every 30 minutes at night. It will thoroughly check your blood pressure to reveal if your blood pressure sometimes becomes too high or too low so that you get right treatment and check if your blood vessels are stiff. We will provide you with transport money to bring the machine back the following day.

5. We will check blood results from the blood taken by your regular caring doctor.

WILL THERE BE ANY INCONVIENCE DURING THE STUDY?

All the tests are harmless and you will be supplied with transport fee.

WITHDRAWAL FROM THE STUDY

You can stop participating in the study at any time for example when you are uncomfortable with questions, tests, researcher, Groote Schuur Hospital.

The investigator has a right to withdraw you from the study if you do not follow the regulations of the study.

ANY DISCOMFORT FROM THE STUDY

No harm is expected from the study

INSURANCE AND FINANCIAL ARRANGEMENTS

In the very unlikely event of you being harmed in the study, the study doctors are covered by insurance. University of Cape Town (UCT) has no fault insurance policy for trial related injuries which states:

"UCT undertakes that in the event of you suffering any deterioration in your health or well-being or from any unexpected sensitivity or toxicity that is caused by participating in the study, it will provide immediate medical care. UCT has appropriate insurance cover to prompt payment of compensation for any trial related injuries according to guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991.

Broadly speaking the ABPI guidelines recommend that the insured company (UCT) without legal commitment, should compensate you without you having to prove that UCT is at fault. Any injuries is considered trial related if and to the extent that is caused by study activities, you must notify the study doctor immediate of any side effects and or injuries during the trial whether they are research related or other related complications.

UCT reserves the right not to provide compensation if and to the extent that your injuries came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of the guidelines are available on request."

ANY ADDITIONAL INFORMATION NEEDED

You will be under the care of doctor Luvuyo Mzingeli and Professor Brian Rayner, please do not hesitate to contact us for more information on 0214043318. Please

also feel free to contact Human Research Ethics Committee c/o Ms Lamees Emjedi at E52 Room 24, Old Main Building, Groote Schuur Hospital, Observatory on 0214066338.

CONFIDENTIALITY

Confidentiality of patient records will be paramount during and after the whole study. All files will be locked away and kept private. Patients will be allocated a code (study number). Investigators involved the study will be the only ones aware of the link between hospital records and study codes.

We will not in way share information about you except to those involved in the research. The information recorded will be analysed and published without revealing the identity of the participants in scientific journals. Research Committee of University of Cape Town and medical Control Council of South Africa will review the results as a regulatory body.

A clinical protocol of the research was submitted and approved by Health Sciences Research Ethics Committee of the University of Cape Town which is registered by National Health Research Ethics Council. The research structure ethical principles are in accordance with the world medical association Declaration of Helsinki 2013 and guidelines on clinical Trials and Ethics in Health Research published by Department of Health.

CERTIFICATE OF CONSENT

I have been invited to participate in the research about RELEVANCE OF MEASURING 24 HOUR AMBULATORY BLOOD PRESSURE, PULSE WAVE VELOCITY AND CENTRAL BLOOD PRESSURE IN KIDNEY TRANSPLANT RECIPIENTS.

I have read the information letter or it has been read to me. I have had opportunity to ask questions about it and questions I asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Name of participant.....

Signature of participant..... date:

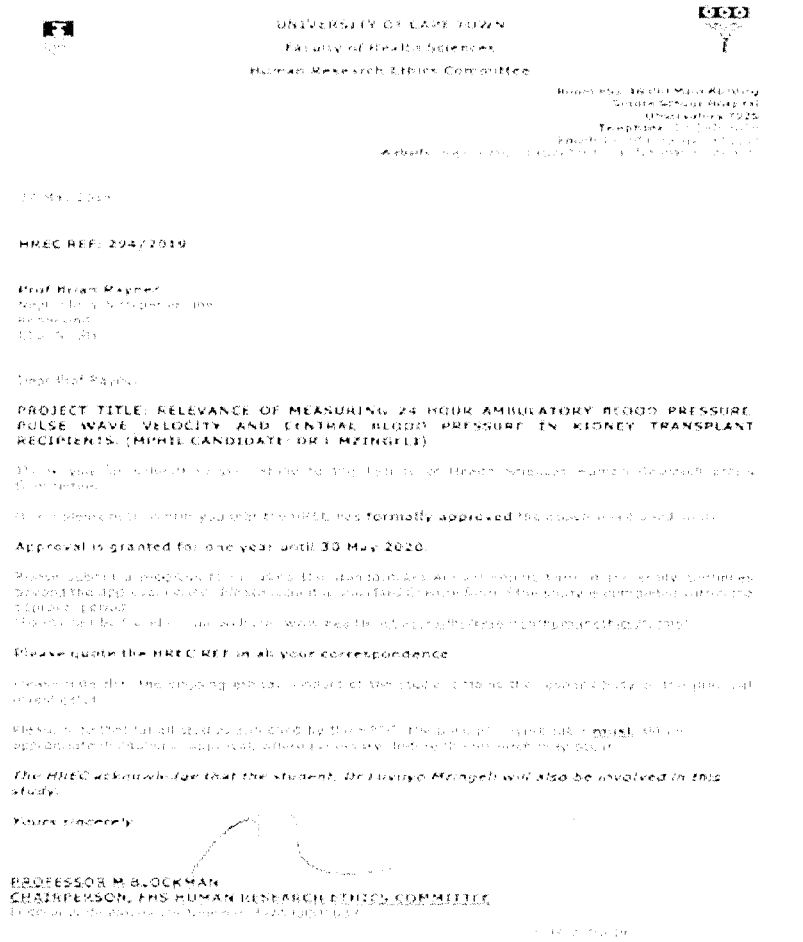
.....

IF ILLITERATE

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness..... Thumb print of witness.....

Signature of witness……



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

HREC REF: 294/2019

Prof Brian Rayner

PROJECT TITLE: RELEVANCE OF MEASURING 24 HOUR AMBULATORY BLOOD PRESSURE, PULSE WAVE VELOCITY AND CENTRAL BLOOD PRESSURE IN KIDNEY TRANSPLANT RECIPIENTS. (MPHIL CANDIDATE: DR T MZINGELI)

formally approved

Approval is granted for one year until 30 May 2020

Please quote the HREC REF in all your correspondence

The HREC acknowledge that the student, Dr Tiwayo Mzingeli will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Reviwers of the paper from Clinical Nephrology suggested the following changes on the manuscript before accepting for publication.

File Edit Format View Help

Methods (pag.6)
Please define stable wat is it ? Are you including as renal function, plasma electrolites, acidosis.
How? Sitting, after 5 min rest, average of 3 stable recording
page 7 - Do you use left or right arm, how do you chose?
page 8 - Please add the list of antihypertinsive drugs used
A more save dat-base recording should be used
Which kind of program was used for statistical analysis

page 9 Results
Please specify kind of steroids and dose were taking per day
page 10 -A table with all data mention should be inserted
Please clarify how central systolic blood pressure was determined
A graph showing the BP differences may help to understand this point, major results of the study.

Dear Brian Rayner

I am pleased to accept your interesting manuscript "THE RELEVANCE OF PERFORMING 24-HOUR AMBULATORY BLOOD PRESSURE AND PULSE WAVE ANALYSIS IN KIDNEY TRANSPLANT RECIPIENTS (Manuscript-ID 110209 - 1)" for publication in Clinical Nephrology.

It has been sent to the publishers and you should receive the galley proofs shortly thereafter.

Thank you for giving us the opportunity for publishing your work.

We would like to take this opportunity to let you know that, as an author of a paper soon to appear in Clinical Nephrology, we may ask you to review papers submitted in your area of expertise. We consider this as an important part of your role as an author. We also invite you to consider Clinical Nephrology as the first repository for future papers.

Yours sincerely,

Dr. Hartmut H. Malluche, MD, Professor and Chief
(Editor-in-Chief)
Peter Sawaya, MD, Professor of Medicine
(Deputy Editor)

Division of Nephrology, Bone and Mineral Metabolism
Department of Internal Medicine
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