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Reproducibility of Ambulatory Blood Pressure Monitoring in Autosomal Dominant Polycystic Kidney Disease

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By

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M.D., Université de Bordeaux-II, 1997

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An abstract of
A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University
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Abstract

Reproducibility of Ambulatory Blood Pressure monitoring (ABPM) in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

By

Frederic F. Rahbari Oskoui, M.D.

Background: Non-dipping defined as less than 10% decline in night/day systolic (SBP) and diastolic blood pressures (DBP) by 24 hour ABPM is associated with poor cardiovascular outcomes in patients with essential hypertension. However, controversies on reproducibility of dipping status have been raised in both essential hypertension and ADPKD. Therefore, we established the short term reproducibility of ABPM in ADPKD.

Methods: 25 HALT-PKD trial participants with estimated glomerular filtration rate (eGFR) > 25 ml/min underwent ABPM on two occasions, 7-15 days apart, after completion of antihypertensive medication titration. Daytime was defined as 6:00-21:59 and night time as 22:00-6:00. Correlation and concordance coefficients for SBP, DBP, mean arterial pressure (MAP), heart rate (HR) and pulse pressure (PP) were determined based on day/night separation of the readings. Dipping was considered both as a dichotomous and continuous variable. Cohen's Kappa statistics were used to compare the proportions of dippers and non-dippers. Univariate analysis was performed to identify potential associations between dipping status and various characteristics.

Results: 29 patients were consented of whom 25 completed two acceptable ABPMs. Mean (±SD) age was 43.12 (8.55) years, age of onset for HBP 33.6 (11.1) years, estimated GFR 63.1 (20.5) mL/min, BMI 26.6 (5.1) Kg/m^2, baseline SBP and DBP were 129.6 (12.5) and 81.6 (6.5) mmHg. Mean (±SD) differences in daytime-nighttime blood pressures were 11.74(8.2) and 10.82 (6.4) mmHg for SBP and DBP respectively.17/25 subjects (68%) were either consistently non-dippers (11/25 or 44%) or consistently dippers (6/25 or 24%). Two (8%) were reverse-dippers. Eight (32%) changed their dipping status between two measurements. The overall Cohen's Kappa statistic was 0.34 (SD=0.18). Correlation and concordance coefficients were 0.881 and 0.887 for daytime SBP, 0.862 and 0.882 for daytime DBP, 0.939-0.897 for nighttime SBP and 0.932-0.887 for nighttime DBP respectively. No variables associated with the magnitude or consistency of dipping.

Conclusion: Repeated measures of SBP and DBP 7-15 days apart are highly correlative and concordant in treated hypertensive ADPKD patients. Non-dipping is present in majority of patients and is moderately reproducible in this population. Future research is warranted to elucidate determinants of nocturnal dipping over a short period of time.

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Table of Contents

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease affecting at least 1/1000live births and up to 12 million people worldwide. ADPKD is due to identified mutations in PKD1 and PKD2 genes and progresses to end stage renal disease (ESRD) at a mean age of 55 years for PKD1 and 69 years for PKD2 patients. Hypertension is common, affecting 60% of patients prior to the development of renal insufficiency, with an early onset (mean age of onset of 31 years and a prevalence rate of up to 22% in pediatric population) and a strong association with increased activity of the renin-angiotensin-aldosterone system (RAAS) at a very early stage (1) (2) (3). Hypertension is the most preventable and treatable associated condition with ADPKD and presents a major risk factor for cardiovascular mortality, the leading cause of death in this population (4). Therefore, blood pressure monitoring is crucial in the management of hypertension in this population.

Blood pressure monitoring can be accomplished through invasive and non-invasive methods. The three most commonly used non-invasive methods include office blood pressure monitoring (OBPM) using oscillometric or aneroid devices, self-measured home blood pressure monitoring (HBPM) using oscillometric devices, and 24-hour Ambulatory blood pressure monitoring (ABPM) using a special oscillometric device. OBPM constitutes the most commonly used method for diagnosis and management of hypertension (5) (6). However, due to the existence of white-coat hypertension (office blood pressures readings higher than home readings) and masked hypertension (home readings higher than office readings), conventional measurements may be unrepresentative of the true blood pressure in about 30% of subjects attending hypertension clinics (7). Therefore, out-of-office blood-pressure monitoring using either 24-hour ABPM or HBPM is often necessary. HBPM and ABPM readings can be equally used to diagnose “white coat” and “masked hypertension” and they have been shown to be more

reproducible and reliable than OBPM (8). They (??) also strongly predict end-organ damage (Left ventricular hypertrophy or LVH, arterial stiffness, albuminuria) in essential hypertension and chronic kidney disease (CKD) (9) (10) (11). Additionally, ABPM has the advantage of providing more blood pressure readings (which may better reflect the true blood pressure) and also giving valuable information on nocturnal and early morning variations of blood pressure compared to HBPM. Lack of nocturnal drop in blood pressure called" non- dipping", despite multitude of definitions used to categorize it, has been associated with end organ damage (left ventricular hypertrophy (LVH), congestive heart failure (CHF), strokes, acute coronary events, all cause mortality, microalbuminuria, decline in glomerular filtration rate (GFR) and progression to end stage renal disease (ESRD) independently of the level of blood pressure, both in essential hypertension and in ADPKD (12) (13) (14) (15)(16) (17) (18) 19) (20) (21). Furthermore, reverse dipping, as defined by night:day ratio >1 has been associated with even worse cardiovascular outcomes (22).

In spite of this cumulative evidence on salutary role of nocturnal dipping, reproducibility of this phenomenon remains controversial. Specifically in ADPKD patients, one study looked at the question of reproducibility of the dipping status in repeated measurements completed in a span of over one year and concluded that there was poor reproducibility of dipping status utilizing ABPM (33%). However, several factors confounded the results of this study, including medication regimen and renal function changes over the lengthy duration between repeat measures (23). Therefore, utility of the main advantage of ABPM over HBPM in providing information on diurnal patterns of blood pressure variability remains uncertain in ADPKD.

We therefore chose to conduct a pilot study to establish reproducibility of ABPM in ADPKD with the following specific aim:

Specific Aim: To establish the reproducibility of ABPM in 25 hypertensive ADPKD subjects

based on two measurements 7-15 days apart, under similar conditions, more than 4 months after randomization in the HALT-PKD trial.

We hypothesized that 24 hour ambulatory blood pressure monitoring is reliable and reproducible in treated hypertensive ADPKD patients, if measurements are repeated under similar conditions.

Background and Significance

Tremendous variability in disease progression has been observed in ADPKD. Independent risk factors for progressive renal disease include presence of hypertension, albuminuria, younger age at diagnosis, male gender, episodes of gross hematuria, PKD1 mutation and increasing renal size (24) (25) (26)

As previously mentioned, treatment of hypertension has a central place in management of ADPKD patients and the location and type of blood pressure monitoring is critical in achieving blood pressure targets. OBPM remains the most commonly used non-invasive method for diagnosis, treatment and follow-up of hypertension (27). Current guidelines for diagnosis and management of hypertension outlined in the 7th report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7) are primarily based on OBPM with some reference to 24 hour ABPM and almost none to self-measured HBPM (5).

Nonetheless, significant differences in blood pressure readings exist between different monitoring modalities and the implications of these differences can be critical in clinical practice. Several studies have quantified the magnitude of difference between BP readings obtained through these modalities, in essential hypertension. Table-1 summarizes the results of 6 studies comparing OBPM, HBPM, and ABPM in essential hypertensive patients (28) (29) (30) (31) (32) (33). Given these differences, one can easily understand that if we applied the blood pressure targets of OBPM to HBP readings, there may be a significant risk of underestimating hypertension and under-treating these patients which would result in increased risk of target organ damage. OBPM readings are usually 7-17 mmHg higher for SBP and 5-14 points higher for DBP compared to ABPM and HBPM (34). The difference between day time ABPM readings and HBPM seem to be insignificant. HBPM is taking a growing place over the two other

modalities due to cost effectiveness, better prediction of cardiovascular outcomes, the strong correlation with daytime ABPM, and the increased therapeutic compliance due to direct involvement of patients in their care (35) (36) (37).

However, ABPM remains the only modality that provides insight into the diurnal variations of blood pressure. Historically, the first evidence for a nocturnal drop in blood pressure came from intra-arterial blood pressure monitoring by Bevan et al in Oxford, UK in 1967 (40). Later, non-invasive methods were used to reproduce the same results (38). The term of dipping and non-dipping was first used by O'Brien et al in 1988 in a purely descriptive fashion (39). The original definition of nocturnal dipping used absolute values of difference between mean diurnal and nocturnal SBP and DBP (10 and 5 mmHg) but night:day ratios quickly replaced that approach in order to take into account the magnitude of the baseline blood pressure. An absolute or relative decrease in different parameters (SBP, DBP), or combination of parameters (SBP+DBP and SBP or DBP) have also been used to categorize this phenomenon. Currently the most commonly used definition of nocturnal dipping is a night:day SBP and DBP ratio of >0.9.

Evidence for utility of nocturnal dipping in prediction of cardiovascular outcomes came later from longitudinal studies, such as the Ohasma study, where non-dipping was strongly associated with poor cardiovascular outcomes (40). Each 0.05 increment in night:day ratio of SBP or DBP corresponded to a 20% increased risk of cardiovascular death in the Japanese cohort, even when blood pressure was adequately controlled (<135/80).

It's only after realizing the association between the dipping status and clinical outcomes that reproducibility of this potential risk stratification tool was investigated. In 1994, Palatini et al reported the first paper on reproducibility of ABPM in the HARVEST trial (41).A year later, James et al reported poor reproducibility of the nocturnal dipping and recommended abandoning this classification (42). Ever since, an ongoing controversy has shadowed the use of dipping

status for clinicians. Parati and Staessen did a thorough review of major articles on short term, midterm and long term reproducibility of dipping status in different populations and showed the conflicting evidence which came out of these studies. (See Table-2) (68)

The data on ABPM is scant in ADPKD. Therefore, significance and reproducibility of non-dipping and the comparative place of ABPM and HBPM are less clear in this population. ABPM is superior to OBPM in diagnosing masked hypertension and prehypertensive states (43). Furthermore, a positive correlation between average 24 h SBP and LVMI has been demonstrated in both normotensive and hypertensive ADPKD patients (19) ADPKD patients also demonstrate lower amplitude of nocturnal dip and higher frequency of non-dipping than essential hypertensive patients (21).

To this date there is only one single study addressing the question of reproducibility of the dipping status has been questioned in ADPKD. Covic et al performed 3 sets of ABPM (at least 3 months apart) within 12 months, in 30 hypertensive ADPKD patients. They reported a consistency of dipping status of 43% between two sets and 36.6% between the three sets (23). However, these results may be confounded by the composition of the population (both hypertensive and normotensive subjects), the different therapeutic regimens and an increase of the mean serum creatinine during the length of the study.

Therefore, establishing reproducibility of ABPM in this population in a more rigorous way remains to be done. Thus, we decided to conduct this pilot study to answer that question.

Methods

Recruitment

Patients were all recruited from HT-PKD trial.

HALT- PKD trial

We used the general infrastructures of the ongoing HALT-PKD trials for recruitment of the subjects. Design and implementation of HALT-PKD trials have extensively been detailed elsewhere (44). In summary, The Polycystic Kidney Disease Clinical Trials Network was developed by the National Institutes of Health (NIH) in 2003 to help support the conduct of randomized clinical trials to determine the efficacy of interventions on slowing the progression of kidney disease in ADPKD. HALT-PKD, sponsored by the National Institutes of Health (NIH) is a combination of two concurrent, randomized, double blinded, placebo-controlled, multicenter trials designed to determine the efficacy of single versus multilevel blockade of the RAAS by using a combination of an Angiotensin converting enzyme Inhibitor (ACE-I) and an Angiotensin receptor blockers (ARB) to ACE-I alone. Home blood pressure monitoring was chosen as the method of choice to guide therapeutic decisions regarding dose titration and addition of new antihypertensive agents. ABPM was not included in the main HALT-PKD trial procedures. Seven major US academic centers were involved as primary clinical centers (PCCs) in recruitment of 1018 patients (254 patients at Emory University) and two data coordinating centers (DCCs) situated at Washington University-St Louis and University of Pittsburgh have consecutively been in charge of the organization of the study, data collection and analysis. After a washout period of 2 weeks, subjects were randomly assigned to increasing doses of ACE-I (Lisinopril) + Placebo versus ACE-I (Lisinopril) + ARB (Telmisartan). Additionally, randomizations assigned patients with eGFR of more than 60 ml/min to two different blood

pressure targets. Standard blood pressure goal was defined as SBP = 120-130 mmHg and DBP= 70-80 mmHg, and aggressive blood pressure goal as BP <110/75 mmHg. Additional lines of treatment included a diuretic, a beta blocker, a calcium channel blocker were introduced as needed. Clinical and laboratory data were periodically checked in participants. Figure-1 shows the main design of the HALT-PKD trial and the place of the pilot ABPM study in the parent study.

Recruitment goals

This pilot study recruited subjects at Emory University and the Mayo clinic, MN. The target recruitment goal was 25 patients.

Inclusion Criteria

1. Age of 18 and 64.
2. Confirmed diagnosis of ADPKD by imaging studies.
3. Hypertension as defined by a BP >130/80 or being on antihypertensive medications.
4. Estimated eGFR based on 4-point MDRD formula >25-60 ml/min
5. Absence of diabetes or another form of kidney disease other than ADPKD.
6. Absence of a history of an adverse reaction to ACE-Inhibitors or ARBs.
7. Absence of congestive heart failure
8. Absence of chronic inflammatory disease or need for immunosuppression
9. Absence of nephrectomy (both study A and B) or cyst reduction surgery (only study A).
10. Absence of claustrophobia or other contraindications to MR-imaging. (only study A).
11. Provide informed consent for this ancillary study.

12. Agreement to ABP monitor placement at the PCC and wearing it for two periods of 24 continuous hours.

13. Absence of allergic reaction to rubber (blood pressure cuff).

14. Absence of acute illnesses.

15. Absence of limited mobility (wheelchair bound or bedridden)

Human Subject Protection

The study protocol was approved by the HALT-PKD steering committee and the Institutional Review Boards (IRB) of Emory University and Mayo clinic. The study was considered "low risk" by those IRBs.

All subjects signed the consent form before any study procedure was started.

Ambulatory blood pressure monitoring procedures

The monitor

Ambulatory BP monitoring was performed using the Spacelab-90207 monitors (Spacelabs-Redmond, WA) which are approved by the British society of hypertension (BSH) and the American association for medical instrumentations (AAMI).

ABP monitor setup and removal

The arm selected for ABP monitoring in the HALT-PKD Study will be the same arm used for blood pressure monitoring in the main HALT-KD trial. The non-dominant arm was preferentially used unless there was a discrepancy of >10 mm Hg between arms in which case the arm with the

higher BP was used. The appropriate cuff size (small, adult, adult plus and large) for each subject was determined based on the markings on the outside of the cuff when it was wrapped around the arm, one inch proximal to the antecubital fossa with no more than one fingerbreadth of space between the skin and the cuff. An index marking indicates the part of the cuff that should lie over the brachial artery. Patients were instructed to wear the monitor for 24 full hours, avoid showering or bathing during that period and resume their normal activities, with the exception that vigorous exercise, as soon as the monitor was placed. They were also instructed to straighten their arms when the monitor was attempting to take the blood pressure. ABPMs were performed both either on a work day or a non-work day for each individual. Patients were provided with a log sheet to record activities throughout the day, including any physical or emotional stressors that might affect BP. The cuffs were cleaned with an alcohol based sterilizing solution between patients. They returned the monitor either in person or through overnight mail delivery and the functioning of the monitor was checked by the study investigator.

Frequency of Measurement

After reaching the F-5 visit (4 Month) and on a stable dose of Lisinopril + Telmisartan/placebo, two ABMP were obtained 7-15 days apart. The monitor was programmed to take a BP measurement every 20 minutes during the day (06:00 to 21:59) and every 30 minutes during the night (22:00 to 05:59). In case of interference during the measurement cycle, the monitor automatically retook the blood pressure up to 3 times until it obtained an acceptable reading. The ABPM is internally calibrated.

ABPM validation criteria

AMBP was deemed to be adequate if the three following criteria were met:

1- Total number of readings > 50/ 24 hours.

2- At least one measurement every hour during the day and every two hours during the night.

3- Less than 10% of erroneous or repeated readings.

Coordinator Training

Coordinators were trained by the principal investigator at each of the two participating PCCs. They were taught to correctly place and remove the ABP device, and upload the data to the PC.

Database management

Demographic and medical data were obtained at each visit of the main HALT-PKD trial. Data from ABPM for the most recent 24-hour study was retrieved and downloaded after each study into the computers and de-identified by using study ID numbers. An EXCEL spreadsheet labeled with the patient's Study ID number and visit was also created for each study. There integrity of compliance with the study protocol was ascertained at each annual site visit by the DCC and reports of progress were presented to the steering committee and Data Safety Monitoring Board of the main HALT-PKD trial on a biannual basis.

Statistical Methods

Description of ABPM parameters

Key parameters of interest, including daytime and night time systolic and diastolic blood pressures were calculated from the 24-hour record according to the following conventional definitions.

1) **Definition of day time and night time:** Daytime was defined between 6:00 AM and 9:59 PM and nighttime between 10:00 PM and 5:59 AM.
2) The average daytime and nighttime systolic and diastolic pressures were calculated as the average of readings over the day and night periods. .
3) **Mean Arterial Pressure** was calculated by adding the diastolic to one-third of the difference between the systolic and diastolic readings.
4) **Heart rate:** Number of heart beats per minute during blood pressure measurements.
5) **Dipping status**: was defined by calculating the night:day ratio of SBP and DBP. Non-dipping was defined as a night:day ratio of both SBP and DBP ≥ 0.9 and dipping as a ratio < 0.9.
6) **Pulse Pressure** is calculated by subtracting the diastolic from the systolic reading.

Sample size and Study Power

A sample size of 25 was determined to be adequate to have 80% power to detect any correlation larger than 0.4 between SBP, DBP, and dipping status comparing the two sets of ABPM, at a significance level alpha 0.05.

Data Analysis

The Division of Biostatistics at University of Pittsburgh provided the baseline patient data from the HALT-PKD trial.

Correlation coefficients (CC) and concordance correlation coefficients (CCC) were determined to compare SBP, DBP, MAP, Heart Rate (HR) and the pulse pressure (PP) between Day-1 and Day-2 (45).

The reproducibility of dipping status was determined by estimating the proportion of patients who remained in the same dipping category. Cohen's Kappa statistics were used to compare those proportions (46). We also considered the night/day ratio of SBP and DBP as continuous variables

and calculated Pearson correlation coefficients for each measure at Day-1 and Day-2. Univariate analysis was performed to look for potential associations between consistency of dipping and predictor variables. Finally we performed univariate analysis between the night:day ratios of SBP (and DBP) and different predictor variables.

Due to the paucity of participants (n=25), logistic or linear regression were not deemed to be applicable since we could not put more than two predictor variables in the model at a time. All data analysis was performed using SAS 9.2 (SAS Institutes Cary, NC)

Results

29 subjects (22 at Emory University and 7 at Mayo clinic) were consented. One subject could not tolerate the blood pressure cuff for more than 45 minutes and withdrew consent. Two others finished the first set of ABPM but didn't come back for the second and a forth one had invalid number of readings over night. 25 subjects successfully completed two adequate sets of ABPM.

The study cohort was composed of middle aged (mean age 43.1 years), non-smoking (96%), non-African-American (92%) predominantly female (52%) participants. They had fairly intact renal function (mean serum creatinine was 1.29 mg/dl and mean eGFR 63. ml/min/1.72 m^2) and hypertension that was diagnosed for a mean 9.6 years that was extremely well controlled at the time of enrollment for ABPM study (mean SBP and DBP 113.6 and 71.7 mmHg respectively). The baseline characteristics are summarized in Table-3.

Blood pressure readings were similar between day-1 and day-2 (Table-4, Figure-2) with an average daytime SBP of 121.9 vs. 120.4 mmHg and average DBP of 77.6 and 77.10 mmHg ($p < 0.05$). Similar findings were present for MAP, HR and PP. The nocturnal decline in SBP and DBP between day-1 and Day-2 were 10.2 vs 8.8 mmHg for SBP and 10.8 vs. 8.6 mmHg for DBP ($p<0.05$). Heart rate did not demonstrate a nocturnal decline in Day-1 or 2

We found strong correlation and concordance between Day-1 and Day-2 SBP, DBP, MAP, and HR. (Correlation coefficients all above 0.77) Concordance coefficient for night time pulse pressure was slightly lower at 0.67 (see Table-5).

Out of 25 subjects, 11 (44%) were non-dippers on both days, 6 (24%) were dippers on both days, 3 (12%) were Non-dippers on day-1 and became dippers on day-2

and 5 (20%) were dippers on day-1 and became non-dippers on day-2. In the non-dipping group, we found 2 (8%) reverse-dippers (one consistently and the other one inconsistently). Overall, 17/25 (68%) subjects stayed in the same dipping category vs 8/25 (32%) who changed their dipping status (See Table-6). The Cohen's Kappa coefficient was calculated at 0.34 (SD = 0.18). The two-sided probability of Kappa = 0 was 0.09.

Univariate analyses using the Fisher's exact test show no significant associations between the consistency of dipping and the following variables; serum creatinine, eGFR, age, duration of hypertension, SBP at F5, DBP at F5, urine aldosterone levels at F5, BMI, caffeine consumption, gender, smoking and race (see Table-7).The same type of univariate analysis did not show any associations between dipping status at Day-1 or Day-2 and the same covariate (results not shown).

When night:day ratios of SBP and DBP were considered as continuous variables, the Pearson correlation coefficients were 0.58 and 0.56 respectively. (See Figure-3)

The univariate analysis didn't show any difference between the Night:Day ratios based on race, CKD stage, gender, age or caffeine intake.

Discussion

Our study is the first one to compare two sets of ABPM in a short interval (<15 days) in a hypertensive ADPKD population on a stable antihypertensive medication regimen. By design, we tried to control certain factors as much as possible. These included renal function, day of the week, and the antihypertensive medication regimen. We showed an excellent correlation and concordance between daytime (and night time) SBP, DBP, MAP and heart rate readings from day-1 to Day-2.

Regarding the nocturnal dipping status, we chose the most restrictive definition that uses the night:day ratios of both SBP and DBP drops (dippers have a ratio of >0.9). Other definitions of nocturnal dipping have been used by different authors and the lack of a universal definition has been proposed as possible explanations for the wide range of reported reproducibility rates of nocturnal dipping (47). These definitions include absolute difference between day and night time average SBP and DBP, night:day ratio of mean SBP, DBP, SBP+DBP, SBP or DBP, use of different cutoff points for definition of day and night (fixed hours vs. diary hours of sleeping), adjustment to level of stress and activity, and removal of the transition hours between day and night in the data analysis (so called narrow fixed time or narrow diary time methods) (47) (48). The lack of uniformity in definitions has been proposed as a possible explanation for lack of reproducibility of the dipping status.

Overall 11/25 (44%) of our patients were consistently non-dippers even when their blood pressure control was optimal. We found 56% and 64% of the subjects to be non-dippers according to the 1st or the 2nd sets of ABPM respectively. This is in contrast with the frequency of non-dipping in essential hypertension which is reportedly between 25 to 42% based on a single measurement (49). Furthermore, we identified two subjects (8%) who presented a pattern of reverse dipping at least once, one of them consistently and another one inconsistently. Reverse-

dipping is associated with even worse cardiovascular outcomes than non-dipping with an estimated frequency of 11% in essential hypertensive population.

We established that the dipping status is reproducible in about 68% of cases when repeated under the same conditions within 7-15 days. This is significantly higher than the previously reported 36.6% consistency over 12 months in PKD population. A kappa value of 0.34 corresponds to a moderate reproducibility (45). Interestingly, our results were almost identical to the ones reported by Ben-Dov et al where they analyzed two ABPM measurements 1-24 months apart in essential hypertension and found 66% consistency of dipping concluding that nocturnal dipping is reproducible (50).

We compared these results, using the fixed-hour separation of day and night (06:00 to 21:59 vs. 22:00 to 05:59) with the self reported sleep-awake times and the results were very similar (results not presented). So we decided to only present the fixed-hour separation data. This is in accordance with previously published literature in day-time workers since we didn't have any night workers in this study and the dairies of our patients did not report any significant episodes of pain or stress that could impact blood pressure readings acutely.

We tried to use a rigorous methodology to repeat the ABPM under same conditions (same day of the week, same medication level, absence of acute illnesses, using the same arm and the same monitor). We excluded subjects who had limited mobility, were night-shift workers, were bedridden, or wanted to heavily exercise. In fact, amplitude of dipping has been shown to be blunted in bedridden patients, suggestingd that body posture (horizontal vs. vertical), and level of activity, and sleep-awake cycles are crucial in determining the nocturnal dipping, rather than a true biological circadian rhythm (51) (52).

In contrast with previously published literature, we couldn't identify any associations between dipping status or consistency of dipping and reported variables such as race, gender, age,

renal function and caffeine intake Possible explanations may include differences due to random chance, misclassification error (ratios of night/day BP of 0.0.8999 vs. 0.901 changes dipping status), potential interference between the use of ACE-I +/- ARBs and the effect of previously reported factors, and the unusually low blood pressure targets that were reached during HALT-PKD trial. In fact, even though non dipping has been associated with poor cardiovascular outcomes independent of blood pressure level, no published studies have reached the level of blood pressures that were achieved in HALT-PKD trial (half of patients were assigned to a BP level of <110/75 and the other half to 120-130/70-80 mmHg).

Our study has its own limitations and the small sample size is the main one, which may directly affect the strength of the evidence that we are presenting and also limited us from using logistic or linear regression models to further elucidate possible explanations for variability of dipping. Also, we could not rule out non-compliance with medications at 100%, but the fact that these patients were extremely motivated volunteers who came on two additional occasions (in addition to the 12-13 required study visits for the main HALT-PKD trail) and had extremely well controlled BP readings, and a good record of drug accountability based on the dispensed and returned number of pills, makes us less suspicious about any major non-compliance issues. Since the design of the protocol was prior to publication of association between urinary sodium excretion and nocturnal dipping, we didn't include 24h urine collection in our study procedures. Selection bias may limit the external validity of our results for other groups of patients with ADPKD, since our study lacked racial diversity and primarily recruited CKD-II and CKD-III patients. We didn't collect information on dietary habits of the patients during the 24 hours of ABPM which might have changed between the two sets of ABPM. We didn't include the data on some of the most recently developed prognostic markers of target organ damage such as the "pressure load" which represents the percentage of readings above a predefined threshold of blood pressure (usually 140/90 mmHg). Since our patients were all treated to very low blood

pressure goals with impressively low pressure loads, we didn't feel the necessity to include that parameter in our analysis.

The apparent paradox between moderate reproducibility of nocturnal dipping and its strong correlation with cardiovascular outcomes remains intriguing. Future research may be directed towards two potential directions. First, determination of an optimal regimen of longer or repeated measurements of ABPM may lead to a better prediction of cardiovascular and renal outcomes. This opinion is supported by limited data suggesting that consistent dipping at least on two occasions is associated with more pronounced cardiac abnormalities than variable dipping in untreated hypertensive patients (53). Also longer ABPM monitoring duration (48 hours) has shown a dramatic 89% consistency of dipping status using the 24-h ABPM (54).[i] We may then use "double dipping" instead of "single dipping" as a better risk stratification strategy. Second, determination of the role of other biological or measurement factors that could potentially explain day-to-day inconsistency of the dipping status can be of additional value in risk stratification of patients. One of these factors could be the day-to-day urinary sodium excretion that has recently been proposed as a possible explanation for changes in dipping status in habitants of the Seychelles Island (predominantly of East African descent) (55). Other potential variables of interest include variation in neurohormonal regulation of blood pressure such as sympathetic nervous activity, endothelial dysfunction, dietary factors other than salt intake (potassium intake, trans fatty acids, etc) and compliance issues with medications (56)(57)(58)(59).

Conclusions

We conclude that measurements of SBP, DBP, PP, MAP and HR are strongly reproducible in treated hypertensive ADPKD patients when the measurements are repeated within a 2 week period of time and under similar conditions. Non-dipping is predominant in this population, even with relatively conserved renal function and excellent blood pressure control. In this population, nocturnal dipping taken both as a dichotomous variable and a continuous variable (night:day ratio of SBP and DBP) is moderately reproducible. Day-to-day variation of the dipping status may reflect underlying biological changes rather than measurement errors. Therefore future studies are needed to elucidate the potential benefit of repeated ABPM measurements in risk stratification of ADPKD patients and also to determine potential factors that may affect day-to-day changes in nocturnal dipping.

Tables

Table-1: Comparisons of OBPM, ABPM and HBPM readings in essential hypertension:

Untreated patients (readings in mmHg)

OBPM	24hABPM	Day ABPM	HBPM	Ref
160/102	141/88	148/92	147/92	(28)
159/102	141/88			(29)
164/103	143/89		150/95	(30)
143/93	132/85		139/89	(31)
142/82	128/76	130/78	135.5/77	(32)
Treatment effect in treated patients (change in BP in mmHg)				
-17/-14	-7/-5		-9/-5	(33)
-22/-14	-15/-10	-17/-11	-16/-10	(28)
-14/-11	-9/-7			(29)
-22/-13	-14/-10		-14/-9	(30)

Table-2: Reproducibility of nocturnal blood pressure fall (reviewed by Parati and Staessen).

Study	Ref	Type of patients	Reproducibility
Palatini et al. (1994)	[41]	Hypertensive	Poor
James et al. (1995)	[42]	Hypertensive elderly	65%
Mochizuki et al. (1998)	[60]	Hypertensive	71%
Omboni et al. (1998)	[61]	Hypertensive untreated or treated	60%
Manning et al. (2000)	[62]	Hypertensive	50%
Covic et al. (2000)	[63]	Hemodialysis	As above
Peixoto et al. (2000)	[64]	Haemodialysis	57%
Rahmana et al. (2005)	[65]	Haemodialysis (6–12 months)	55–70%
		Nondipping	92%
Chaves et al. (2005)	[66]	Normotensive/Treated hypertensive (dichotomous variable)	Poor
		(nocturnal dipping as a continuous variable)	High
Ben-Dov et al. (2005)	[50]	Hypertensive accounting for sleep and awake periods	66%
Cuspidi et al. (2006)	[67]	Diabetic Hypertensive	84.6% (dipper)
			91.3% (Non-D)
		Non-diabetic hypertensive	49.2% (dipper)
			29.5% (Non-D)
Hernandez-del Rey (2007)	[54]	Hypertensive general practice (24h)	76%
		Hypertensive general practice (48 h ABPM)	89%

Table-3: Baseline characteristics

Characteristics	All patients N=25 Mean (SD)
Gender (% Male)	48%
Race (% Non-African American)	92%
BMI (Kg/m2)	26.6 (5.1)
Age at baseline (years)	43.1 (8.6)
Age of onset of HTN (years)	33.6 (11.1)
Duration of HTN (years)	9.6 (10.6)
eGFR (mL/min/1.73 m2 of BSA)	63.1 (20.5)
Creatinine (mg/dL)	1.29 (0.45)
Smoking (% active smokers)	4%
Caffeine (% drinkers)	76%
Office F-5 SBP	113.55 (8.7)
Office F-5 DBP	71.7 (8.8)
Serum Potassium (meq/dL)	4.1 (0.36)
Medication (% of patients on <2 meds)	76%
Urine Aldosterone Baseline	9.7 (4.2)
Urine Aldosterone F5	6.9 (5.5)

Table-4: Comparison of Blood pressure readings between day-1 and Day-2 during day and night.

	Day-1			Day-2		
	Day	**Night**	**Day-Night**	**Day**	**Night**	**Day-Night**
SBP (mmHg)	121.9 (9.6)	111.6 (12.5)	10.2 (10.5)	110.1 (11.14)	8.8 (9.5)	8.8(9.5)
DBP (mmHg)	77.6 (8.4)	68.5 (10.3)	10.8 (7.3)	77.10 (9.1)	66.8 (8.8)	8.6(8.3)
MAP (mmHg)	92 (8.4)	83.3 (10.8)	11 (7.2)	91.61 (9)	80.9 (9)	8.3 (8.6)
HR (Beats/min)	73 (10.8)	63.8 (11.2)	11.3 (7.2)	71.6 (9.5)	61.7 (9.9)	7.9 (7.4)
PP (mmHg)	44.3 (6.4)	43 (5.9)	0.9 (4.2)	43.3 (7)	43.4 (7.3)	0.3 (4.4)

SBP : Systolic Blood Pressure DBP: Diastolic Blood pressure MAP: Mean Arterial Pressure

HR: Heart rate PP: Pulse Pressure

Note: No statistically significant difference between individual values of each parameter at Day-1 AND Day-2.

Table-5: Correlation and concordance coefficients between day-1 and day-2 for daytime and nighttime.

	Correlation coefficients		Concordance coefficients	
	Day	**Night**	**Day**	**Night**
SBP	**0.89**	**0.79**	**0.88**	**0.77**
DBP	**0.91**	**0.81**	**0.91**	**0.81**
MAP	**0.91**	**0.82**	**0.90**	**0.80**
HR	**0.79**	**0.73**	**0.85**	**0.86**
PP	**0.87**	**0.85**	**0.78**	**0.67**

SBP : Systolic Blood Pressure DBP: Diastolic Blood pressure MAP: Mean Arterial Pressure

HR: Heart rate PP: Pulse Pressure

Table-6: Dipping status, day-1 and Day-2

		Day-2		
		Non-Dippers	**Dippers**	**Total**
		n (%)	**n (%)**	**n (%)**
Day-1	**Non dippers**	11 (44%)	3 (12%)	14(56%)
	Dippers	5 (20%)	6 (24%)	11 (44%)
	Total	16 (64%)	9 (36%)	25 (100%

Cohen's Kappa= 0.34 (SD=0.18)

Table-7: Univariate analysis evaluating consistency of dipping status at Day-1 and Day-2 and potential predictor variable.

Variable	Inconsistent dipping Mean (SD) (p-value) n=8	Consistent dipping Mean (SD) n=17	Fisher
Creatinine (meq/l)	1.47 (0.54)	1.2 (0.39)	0.55
Sex (% females)	37.5 %	58%	0.41
Race * (% of Caucasians)	75%	100%	0.09
eGFR (ml/min/1.72 m2)	58.39 (25.49)	65.28 (18.09)	1
Duration of HTN (years)	8.88 (9.96)	9.88 (11.11)	0.61
Age (years)	45 (5.4)	42.24 (9.71)	0.92
Baseline Office SBP (mmHg)	115.62 (7.6)	112.52 (9.31)	0.79
Baseline Office DBP (mmHg)	74.6 (5.96)	70.24 (9.77)	0.91
BMI (kg/cm2)	29.9 (1.89)	24.89 (5.41)	1
Medication (step doses)	3.5 (2.07)	2.47 (1.74)	0.89
Caffeine drinkers (%)	87.5%	76%	1
Smokers (%)**	0	6 %	0.41
Baseline urinary			
Aldosterone (ng/ml)	7.34 (7.8)	6.75 (4.31)	1
Serum Potassium (mEq/l)	4.23 (0.39)	4.06 (0.34)	0.1

eGFR: estimated Glomerular Filtration Rate **HTN: Hypertension**

SBP: systolic Blood Pressure **DBP: diastolic Blood pressure** **BMI: Body Mass Index**

***Only 2 African-Americans**

****** **Only one non-smoker**

Figures

Figure-1: Place of the pilot ABPM in HALT-PKD trial

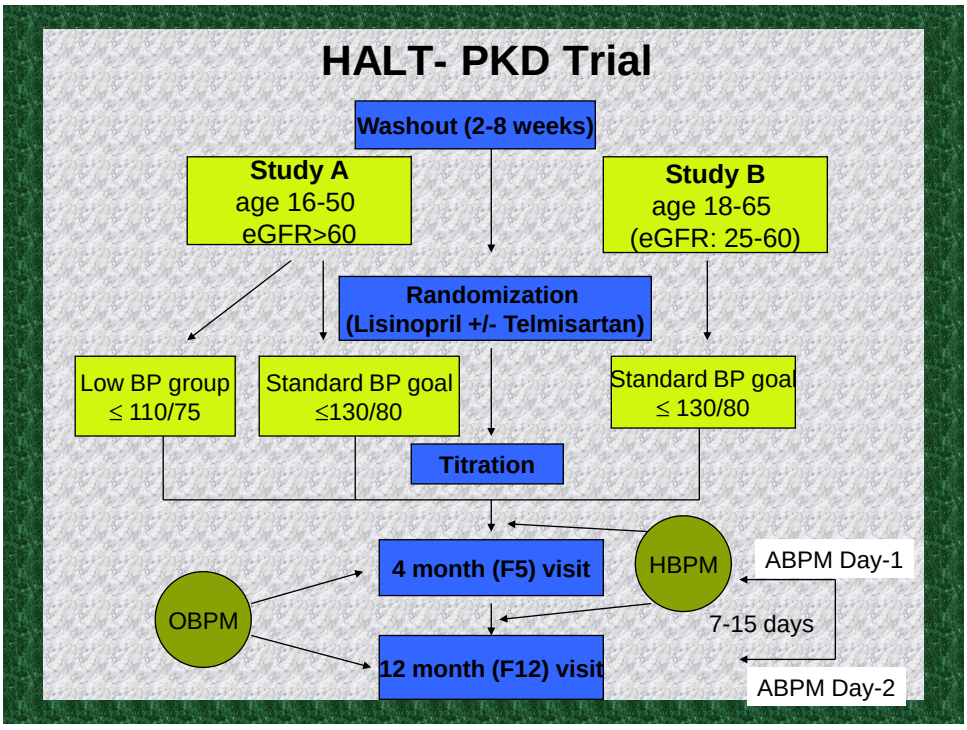


Figure-2: Comparison of Blood pressure readings between day-1 and Day-2

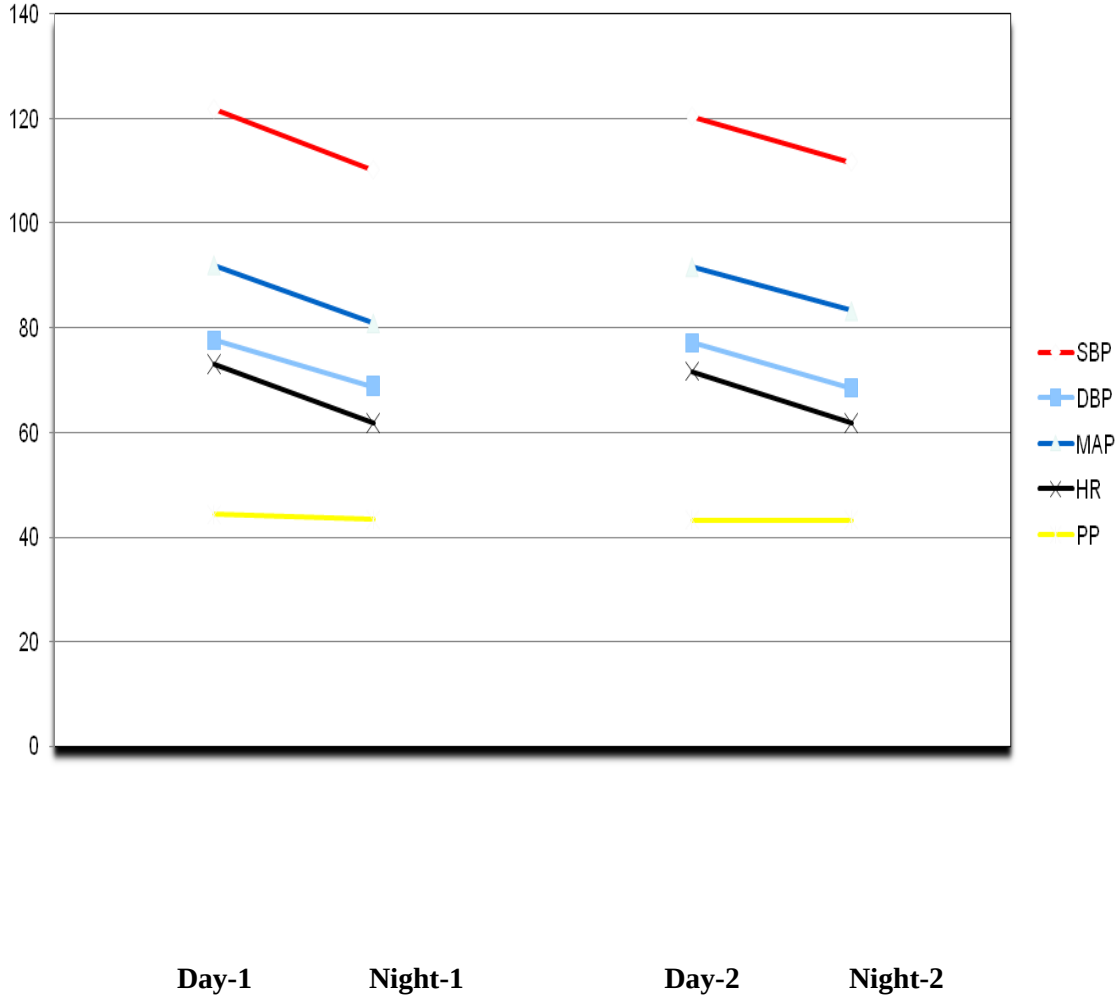
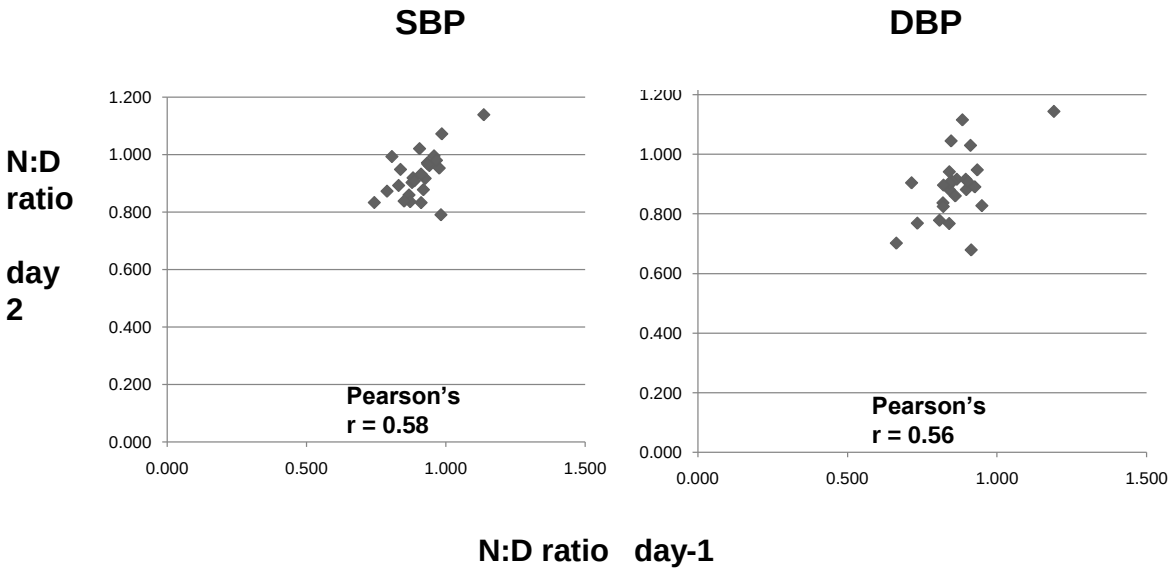


Figure-3: Correlation between night:day ratios of SBP and DBP between Day-1 and Day-2



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List of Abbreviations

AAMI	American Association for Medical Instrumentations
ABPM	Ambulatory Blood Pressure Monitoring
ACE-I	Angiotensin Converting Enzyme Inhibitor
ADPKD	Autosomal Dominant Polycystic Kidney Disease
ARB	Angiotensin Receptor Blocker
BP	Blood Pressure
BSH	British Society of Hypertension
CC	Correlation Coefficient
CCC	Concordance Correlation Coefficient
CHF	Congestive Heart Failure
DCC	Data Collecting Centers
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
HBPM	Home Blood Pressure Monitoring
HR	Heart rate
IRB	Institutional Review Board
LVH	Left ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
MAP	Mean Arterial Pressure
NIH	National Institutes of Health

OBPM	Office Blood Pressure Monitoring
PCC	Primary Clinical Centers
PP	Pulse Pressure
RAAS	Renin-Angiotensin-Aldosterone System
SBP	Systolic Blood Pressure