



ORIGINAL ARTICLE

Ambulatory blood pressure trajectories and blood pressure variability in kidney transplant recipients: a comparative study against haemodialysis patients

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ABSTRACT

Background. Hypertension is the most prevalent cardiovascular risk factor in kidney transplant recipients (KTRs). Preliminary data suggest similar ambulatory blood pressure (BP) levels in KTRs and haemodialysis (HD) patients. This is the first study comparing the full ambulatory BP profile and short-term BP variability (BPV) in KTRs versus HD patients. **Methods.** A total of 204 KTRs were matched (2:1 ratio) with 102 HD patients for age and gender. BP levels, BP trajectories and BPV indices over a 24-h ambulatory BP monitoring (ABPM) in KTRs were compared against both the first and second 24-h periods of a standard 48-h ABPM in HD patients. To evaluate the effect of renal replacement treatment and time on ambulatory BP levels, a two-way ANOVA for repeated measurements was performed. **Results.** KTRs had significantly lower systolic blood pressure (SBP) and pulse-pressure (PP) levels compared with HD patients during all periods studied (24-h SBP: KTR: 126.5 ± 12.1 mmHg; HD first 24 h: 132.0 ± 18.1 mmHg; $P = 0.006$; second 24 h: 134.3 ± 17.7 mmHg; $P < 0.001$); no significant differences were noted for diastolic blood pressure levels with the exception of the second nighttime. Repeated measurements ANOVA showed a significant effect of renal replacement therapy modality and time on ambulatory SBP levels during all periods studied, and a significant interaction between them; the greatest between-group difference in BP (KTRs–HD in mmHg) was observed at the end of the second 24 h [-13.9 mmHg (95% confidence interval -21.5 to -6.2); $P < 0.001$]. Ambulatory systolic and diastolic BPV indices were significantly lower in KTRs than in HD patients during all periods studied (24-h SBP average real variability: KTRs: 9.6 ± 2.3 mmHg; HD first 24 h: 10.3 ± 3.0 mmHg; $P = 0.032$; second 24 h: 11.5 ± 3.0 mmHg; $P < 0.001$). No differences were noted in dipping pattern between the two groups.

Received: 26.8.2021; Editorial decision: 7.12.2021

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Conclusions. SBP and PP levels and trajectories, and BPV were significantly lower in KTRs compared with age- and gender-matched HD patients during all periods studied. These findings suggest a more favourable ambulatory BP profile in KTRs, in contrast to previous observations.

Keywords: ambulatory blood pressure monitoring, blood pressure variability, end-stage kidney disease, haemodialysis, kidney transplantation

INTRODUCTION

Hypertension is the most common modifiable risk factor in patients with chronic kidney disease (CKD), with a prevalence progressively increasing with advancing CKD stages [1]. Kidney transplantation is considered the treatment of choice for patients with end-stage kidney disease (ESKD) as it is associated with a survival benefit compared with patients undergoing haemodialysis (HD) and peritoneal dialysis (PD), mainly attributed to a decreased incidence of cardiovascular disease (CVD) [2]. However, the risk of cardiovascular events remains significantly higher in kidney transplant recipients (KTRs) compared with the general population [3]; also, the high prevalence of hypertension in these patients (70–90%) [4] and its strong association with cardiovascular morbidity and mortality [2] explain a large part of these adverse associations [2, 4, 5].

The use of ambulatory blood pressure monitoring (ABPM) is currently considered the gold standard for the diagnosis and treatment of hypertension in the general population and patients with CKD, due to a number of advantages, including a higher prognostic value compared with office blood pressure (BP), evaluation of the circadian BP pattern and the identification of phenotypes of hypertension (i.e. masked and white coat hypertension) [6, 7]. Another advantage of ABPM is its ability to estimate the short-term BP variability (BPV), a haemodynamic parameter that in recent years has emerged as an independent risk factor for cardiovascular events and mortality in patients with CKD, above and beyond BP levels [8]. Based on such findings, all recent recommendations on hypertension management advocate the wider use of ABPM in patients with CKD [9–12].

In recent years, several studies using ABPM in KTRs have provided very interesting findings, including a high prevalence of nocturnal hypertension and an abnormal dipping profile [13, 14], a strikingly high rate (35–40%) of masked hypertension [15, 16] as well as a large difference between the office and the ambulatory BP control rates at any studied threshold [16]. In addition, a considerable amount of evidence summarized in a recent systematic review and meta-analysis clearly suggests that in KTRs, ambulatory BP has a much stronger association than office BP with both renal function decline and cardiovascular target-organ damage [17].

Although clinical experience and previous studies with office BP suggest the improvement of BP with kidney transplantation, as of this writing, scarce data could be obtained from small studies comparing KTRs and HD patients with ABPM, showing generally similar BP levels [18, 19]. Importantly, such studies only examine average BP levels, which is not the most comprehensive approach, especially since KTRs show major ambulatory BP abnormalities, as described above. As there are currently no data on differences in ambulatory BP trajectories during a typical 24-h period in KTRs and a 24-h or a full 48-h interdialytic period in patients undergoing HD, nor relevant comparisons of the short-term BPV, the aim of this study was to compare for the first time the full ambulatory BP profile, as well as indices of the short-term BPV, in KTRs versus HD patients.

MATERIALS AND METHODS

Study design

This study recruited KTRs and patients undergoing HD under a regular follow-up at the University Nephrology and Renal Transplantation Department in Athens and the University Nephrology Department with its affiliated HD units in Thessaloniki, Greece. We included as cases stable adult patients (>18 years) with ESKD who had received a kidney transplant at least 3 months ago. KTRs (cases) were matched by a blinded member of our group with potential controls from a large cohort of HD patients who were on standard thrice-weekly HD treatment in the first or second shifts. Matching was performed for age (± 5 years) and gender in a 2:1 ratio, following the concept of flexible matching with varying proportions to increase the power and efficiency of the study [20]. Exclusion criteria consisted of (i) estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m² or an eGFR decline $> 30\%$ during the last 3 months for KTRs; (ii) chronic atrial fibrillation or other arrhythmia that could interfere with proper ABPM recording; (iii) the presence of non-functional arteriovenous fistulae that could interfere with proper ABPM recording; (iv) the modification of antihypertensive treatment during the previous 6 weeks (KTRs) or the modification of dry-weight or antihypertensive treatment during the previous 4 weeks (HD patients); (v) myocardial infarction, angina pectoris or stroke during the last 3 months; (vi) history of malignancy or any other condition with poor prognosis; and (vii) pregnancy. The study protocols for the two individual cohorts were approved by local Institutional Review Boards. All evaluations were performed according to the declaration of Helsinki (2013 Amendment), and all participants provided informed written consent prior to participation.

Data collection

All KTRs were evaluated during a scheduled morning visit at the Renal Transplantation Outpatient Clinic in collaboration with the Cardiovascular Prevention & Research Unit of the Department of Pathophysiology of Medical School of National & Kapodistrian University of Athens, while patients undergoing HD were evaluated 1 h before a mid-week (i.e. the second or third weekly) dialysis session (HD patients) in order to cover a typical 2-day interdialytic interval. Demographics, anthropometric characteristics, cause of ESKD, comorbidities and concomitant medications, as well as routine haematological and biochemical parameters, were collected for each participant and recorded in a purpose-built electronic datasheet. Office BP readings in KTRs and pre-dialysis BP readings in HD patients were performed according to guidelines [10].

The ABPM was planned for 24 h in KTRs and for 48 h in HD patients, starting with the beginning of the dialysis session. For patients undergoing HD, the 48-h ABPM was divided into two 24-h periods, with the first 24-h period including the dialysis session and the first day of the interdialytic interval, while the second

24-h period corresponded to the second day of the interdialytic interval. During ABPM, all participants were instructed to continue their regular medication and follow their usual activities.

Ambulatory BP was measured with the Mobil-O-Graph NG (IEM, Stolberg, Germany), an oscillometric device, whose brachial BP-detection unit was validated according to standard protocols and was shown to provide practically identical values to a widely used ABPM monitor [21]. For patients undergoing HD or for KTRs with a functioning fistula, the ABPM device was placed on the opposite arm with a cuff of appropriate size and was programmed to record BP, as previously described [22, 23]. For patients dialysing in the first dialysis shift, the start of the first 24-h period coincided with the start of the daytime (7:00 am to 10:59 pm) and the daytime periods included consecutive hours. For patients dialysing in the second dialysis shift, the daytime periods did not include consecutive times and the daytime of the first 24-h was considered the time between 12:00 noon and 10:59 pm, followed by the time of the following morning between 07:00 am and 11:59 am, as previously described [22, 23]. The nighttime periods for the first and second 24-h periods were constant for all patients (11:00 pm to 6:59 am). In order to minimize the possible effect of manual BP measurements, this analysis included only measurements recorded at the pre-specified time intervals at which the device was set to take measurements (not including manual readings performed by the patients). The raw ABPM dataset obtained from each patient was exported to an Excel file. Separate Excel files were built for each of systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP), where each column represented a recording at a pre-specified time-point (i.e. 07:00 am, 07:20 am, and so on), and each line represented data for each patient. Average values for every time-point were calculated for KTRs and HD groups and were transformed into graphic depictions by Excel.

The BPV indices [weighted standard deviation (wSD) and average real variability (ARV)] were evaluated on the basis of data obtained from the Mobil-O-Graph recordings according to formulas described previously [22, 23] and presented in Supplementary data, Table S1. The dipping pattern of nocturnal BP was calculated with the following formula: $1 - \text{mean night/mean day ratio of SBP (\%)}$. Patients were divided into four categories: (i) extreme dippers (nocturnal BP fall of $>20\%$); (ii) dippers (fall of $>10\%$ and $\leq 20\%$); (iii) non-dippers (fall of $\geq 0\%$ and $\leq 10\%$); and (iv) reverse dippers (nocturnal increase in SBP).

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean \pm standard deviation (SD) or as median (interquartile range) according to the normality of the distribution, examined with the Kolmogorov–Smirnov test for samples ≥ 50 and Shapiro–Wilk test for samples < 50 . Categorical variables are presented as absolute frequencies and percentages ($n, \%$). Between-group comparisons for continuous variables were performed with the independent t-test or the Mann–Whitney test, where applicable, and Chi-squared tests were used for comparisons of categorical variables. Due to the established BP differences between the first (dialysis-on day) and second (dialysis-off day) 24-h periods of a typical 48-h interdialytic interval in HD patients [22, 24], for reasons of completeness, we examined separately differences in the 24-h ABPM recording in KTR patients with the dialysis-on and the dialysis-off days of HD patients. To evaluate the effect of the renal re-

placement therapy (RRT) modality and time on the trends of ambulatory BP levels and to determine whether an interaction between the two existed, we compared the mean hourly values of SBP and DBP between KTRs and HD patients using a two-way mixed ANOVA for repeated measurements for the two 24-h periods. The Greenhouse–Geiser correction was applied to overcome the violation of the sphericity assumption. When a significant interaction between time and RRT type was observed, Bonferroni-adjusted *post hoc* tests were performed. Probability values of $P < 0.05$ (two-tailed) were considered statistically significant for all comparisons.

RESULTS

Demographic and clinical characteristics of KTRs and HD patients

Table 1 presents demographic characteristics, RRT (total dialysis and transplantation) vintage, comorbidities, antihypertensive treatment, immunosuppressive medication and main laboratory data of study participants. No differences were noted between the 204 KTRs and 102 HD patients for age and sex. As expected, KTRs had a longer total RRT vintage compared with HD patients [133.8 (57.3–201.6) months versus 46.4 (28.0–201.3) months; $P < 0.001$]. Importantly, there were no differences between the two groups with regard to BMI and history of hypertension and diabetes. Dyslipidemia was more common, and coronary heart disease (CHD) (9.8% versus 18.6%; $P = 0.029$) and stroke were less common in KTRs. Patients in the renal transplant group had a significantly lower office SBP (129.0 ± 16.9 versus 145.1 ± 21.9 mmHg; $P < 0.001$) and DBP levels (76.5 ± 10.2 versus 90.3 ± 14.2 mmHg; $P < 0.001$) compared with the HD group. This corresponded to a significantly higher total number of antihypertensive drugs (KTRs: 1.7 ± 1.1 ; HD: 1.4 ± 1.1 ; $P = 0.033$) and the use of angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs) (41.7% versus 28.4%; $P = 0.024$) and β -blockers ($P = 0.020$) in KTRs, nitrates ($P = 0.007$), central-acting-agents ($P = 0.019$) and diuretics ($P = 0.011$). Among laboratory parameters, as expected, haemoglobin levels were significantly lower and the concentrations of potassium, phosphorus and parathyroid hormone (PTH) [69.7 pg/mL (50.3–110.5) versus 174.5 pg/mL (305.0–452.0); $P < 0.001$] were significantly higher in the HD group.

Comparison of ambulatory BP levels between KTRs and HD patients over the dialysis-on and the dialysis-off days

Table 2 presents mean ambulatory values for SBP, DBP and PP in KTRs and HD patients and the relevant P-values for comparisons between the 24-h ABPM recording in KTRs and either the first (dialysis-on) or the second (dialysis-off) 24-h period in HD patients. As noted in the table, 24-h SBP was lower in KTRs (126.5 ± 12.1 mmHg) compared with either the first 24 h (132.0 ± 18.1 mmHg; $P = 0.006$) or the second 24 h (134.3 ± 17.7 mmHg; $P < 0.001$) of the recording in HD patients. Similar differences were evident for daytime and nighttime SBPs. With regard to DBP, ambulatory levels were numerically lower in KTRs over all periods studied, but the relevant comparisons reached statistical significance during the second nighttime (Table 2). PP levels were lower in KTRs than HD patients over all periods studied (24-h KTRs: 45.4 ± 8.3 mmHg; first 24-h HD: 49.0 ± 12.3 mmHg; $P = 0.008$; second 24-h HD: 51.0 ± 12.2 mmHg; $P < 0.001$). As expected, most BP

Table 1. Characteristics of study participants

Variable	KTRs (n = 204)	HD (n = 102)	P-value
Female gender (n, %)	68 (33.0)	34 (33.0)	1.000
Age (years)	51.8 ± 12.8	53.4 ± 11.3	0.277
Time since RRT initiation (months)	133.8 (57.3–201.6)	46.4 (28.0–201.3)	<0.001
eGFR CKD-EPI (mL/min/1.73 m ²)	57.9 ± 19.4		
BMI (kg/m ²)	25.4 (23.0–28.4)	24.8 (22.0–27.0)	0.053
Hypertension (n, %)	185 (90.7)	96 (94.1)	0.302
Diabetes (n, %)	36 (17.6)	14 (13.7)	0.382
Dyslipidemia (n, %)	107 (52.5)	23 (22.8)	<0.001
CHD (n, %)	20 (9.8)	19 (18.6)	0.029
Stroke (n, %)	2 (1.0)	19 (18.6)	<0.001
PAD (n, %)	6 (2.9)	6 (5.9)	0.224
Office SBP (mmHg)	129.0 ± 16.9	145.1 ± 21.9	<0.001
Office DBP (mmHg)	76.5 ± 10.2	90.3 ± 14.2	<0.001
Number of antihypertensive drugs	1.7 ± 1.12	1.40 ± 1.10	0.033
ACEi/ARBs (n, %)	85 (41.7)	29 (28.4)	0.024
CCBs (n, %)	823 (40.7)	43 (42.2)	0.805
MRAs (n, %)	0	0	
β-blockers (n, %)	136 (66.7)	54 (52.9)	0.020
α-blockers (n, %)	2 (1.0)	0 (0.0)	1.000
Nitrates (n, %)	2 (1.0)	7 (6.9)	0.007
Central acting agents (n, %)	16 (7.8)	17 (16.7)	0.019
Diuretics (n, %)	22 (10.8)	22 (21.6)	0.011
Statins (n, %)	73 (35.8)	30 (29.4)	0.266
Number of immunosuppressive drugs	2.8 ± 0.4		
Tacrolimus (n, %)	164 (80.8)		
Cyclosporine (n, %)	28 (13.8)		
mTORi (n, %)	19 (9.4)		
MMF/MPA (n, %)	188 (92.6)		
Azathioprine (n, %)	3 (1.5)		
Corticosteroids (n, %)	165 (81.3)		
Hb (g/dL)	13.0 ± 1.6	11.5 ± 1.4	<0.001
Na (mEq/L)	140.4 ± 2.8	137.6 ± 3.3	<0.001
K (mEq/L)	4.5 ± 0.5	5.0 ± 0.6	<0.001
Ca (mg/dL)	9.6 ± 0.5	9.1 ± 0.7	<0.001
Phosphorus (mg/dL)	3.1 ± 0.7	5.1 ± 1.4	<0.001
Ferritin (ng/mL)	207.0 (103.8–393.7)	341.5 (229.3–910.0)	<0.001
PTH (pg/mL)	69.7 (50.3–110.5)	174.5 (305.0–452.0)	<0.001

Data are presented as median (interquartile range) or mean ± SD, unless otherwise indicated.

BMI: body mass index; CCB: calcium channel blocker; CKD-EPI: chronic kidney disease epidemiology collaboration; eGFR: estimated glomerular filtration rate; MMF/MPA: mycophenolate mofetil/mycophenolic acid; MRA: mineralocorticoid receptor antagonist; mTORi: mechanistic target of rapamycin inhibitor; PAD: peripheral arterial disease.

P < 0.05 is considered statistically significant, indicated in bold.

parameters studied were higher in the second versus the first 24-h period in HD patients.

Trajectories of ambulatory BP in KTRs and HD patients over the dialysis-on and the dialysis-off days

The trajectories of hourly mean SBP, DBP and PP levels from 09.00 am to 08.59 am during a 24 h recording in KTRs and the first and second 24-h periods of a 48 h monitoring in patients undergoing HD are depicted in Figures 1, 2 and 3, respectively. As shown in Figure 1A, SBP followed a different pattern in KTRs compared with HD patients. A morning 'SBP surge' was observed in KTRs, followed by a gradual decrease in SBP levels until the afternoon, whereas in HD patients, a gradual decrease was observed in the morning of the first 24-h period (coinciding with the dialysis session in patients dialysing in the first shift) and the early afternoon hours (coinciding with the dialysis session in patients dialysing in the second shift). With the exception of

the first 2 h in the morning (09.00–11.00 am), patients in the HD group had higher SBP levels compared with the renal transplant group. With regard to the second 24-h period (Figure 1B), corresponding to the dialysis-off day in HD, an almost-parallel course of SBP trajectories was shown, with higher SBP levels noted in patients under HD over time. Smaller differences over time were observed in the respective DBP trajectories. During the first 24-h period after 06:00 pm (end of the dialysis session), DBP was almost similar in HD and KTR patients; during the second 24-h period, DBP moved to higher levels in HD patients, especially over nighttime (Figure 2). Finally, with regard to PP, as expected, patients under HD had numerically higher PP levels compared with KTRs during both 24 h and daytime and nighttime periods (Figure 3).

Supplementary data, Figures S1 and S2 present comparisons of the trajectories of hourly mean SBP/DBP levels in KTRs against the first 24 h of the recording in patients dialysing in the first and the second dialysis shifts, respectively, to better

Table 2. Ambulatory BP values during the 24-h ABPM, and the respective daytime and nighttime periods, in KTRs were compared with the relevant values of the first and second 24-h periods of the typical interdialytic interval in patients undergoing HD

Variable	KTRs (n = 204)	HD (first 24 h) (n = 102)	P-value (KTRs versus first 24-h HD patients)	HD (second 24 h) (n = 102)	P-value (KTRs versus second 24-h HD patients)	P-value (HD first versus second 24-h periods)
24-h SBP	126.5 ± 12.1	132.0 ± 18.1	0.006	134.3 ± 17.7	<0.001	0.004
Daytime SBP	127.2 ± 12.2	133.2 ± 17.6	0.002	135.3 ± 18.1	<0.001	0.027
Nighttime SBP	123.9 ± 14.5	128.8 ± 21.2	0.038	132.2 ± 18.6	<0.001	0.001
24-h DBP	81.1 ± 8.4	82.9 ± 11.6	0.160	83.4 ± 11.3	0.078	0.397
Daytime DBP	82.1 ± 8.6	84.3 ± 11.2	0.080	84.4 ± 11.5	0.072	0.853
Nighttime DBP	77.6 ± 9.2	78.9 ± 14.1	0.404	80.5 ± 12.0	0.035	0.031
24-h PP	45.4 ± 8.3	49.0 ± 12.3	0.008	51.0 ± 12.2	<0.001	<0.001
Daytime PP	45.1 ± 8.3	48.8 ± 12.4	0.007	50.9 ± 12.4	<0.001	<0.001
Nighttime PP	46.3 ± 9.6	49.7 ± 13.2	0.021	51.5 ± 12.7	<0.001	0.007

Data are presented as mean ± SD.

P < 0.05 is considered statistically significant, indicated in bold.

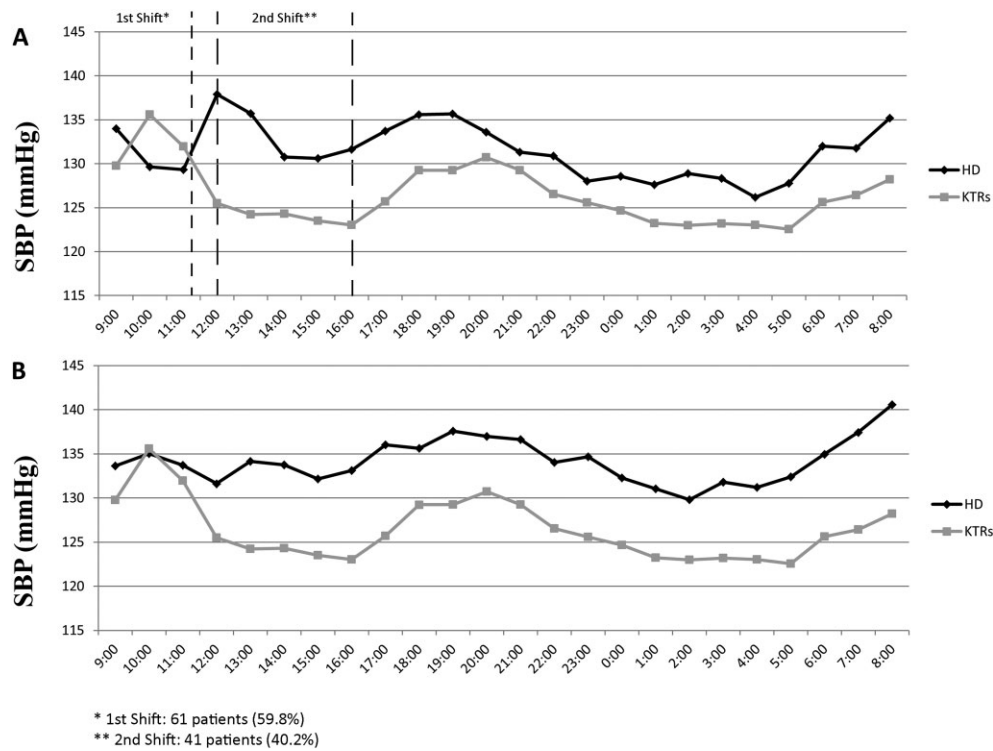


FIGURE 1: Trajectories of hourly mean SBP levels from 09.00 am to 08.59 am during a 24-h recording in KTRs and the (A) first and (B) second 24-h periods of a 48-h monitoring in patients undergoing HD.

illustrate the impact of dialysis sessions on the overall comparative BP profile.

Concerning the results of a two-way ANOVA for repeated measurements of SBP for the first 24 h, there was a significant effect of time [$F(18, 4698) = 11.34, P < 0.001$; partial $\eta^2 = 0.042$] and RRT type [$F(1, 261) = 6.12, P = 0.014$; partial $\eta^2 = 0.023$] on SBP levels. A significant interaction between time and RRT type was also found [$F(18, 4698) = 1.98, P = 0.036$; partial $\eta^2 = 0.008$] with Bonferroni-adjusted *post hoc* tests, revealing that in the majority of different time-points in the first 24 h, except from 08.00 pm to 01.59 am, from 03.00 to 04.59 am and from 07.00 to 07.59 am, patients undergoing HD had significantly higher SBP levels than KTRs. With regard to the second 24 h, there was a significant

effect of time [$F(23, 2898) = 5.92, P < 0.001$; partial $\eta^2 = 0.045$] and RRT type [$F(1, 126) = 7.89, P = 0.006$; partial $\eta^2 = 0.059$] on SBP levels. Notably, a significant interaction between time and RRT type was observed [$F(23, 2898) = 2.34, P = 0.006$; partial $\eta^2 = 0.019$] with Bonferroni-adjusted *post hoc* tests, revealing that across several time-points in the second 24 h, except from 10.00 am to 12.59 pm, from 06.00 to 06.59 pm, from 08.00 to 08.59 pm, from 03.00 to 03.59 am and from 06.00 to 06.59 am, patients undergoing HD had significantly higher SBP levels compared with KTRs, with the greatest between-them difference at 08.00–08.59 am [−13.9 mmHg (95% confidence interval −21.5 to −6.2); $P < 0.001$] (Table 3). Results of a two-way ANOVA for repeated measurements for ambulatory DBP are presented

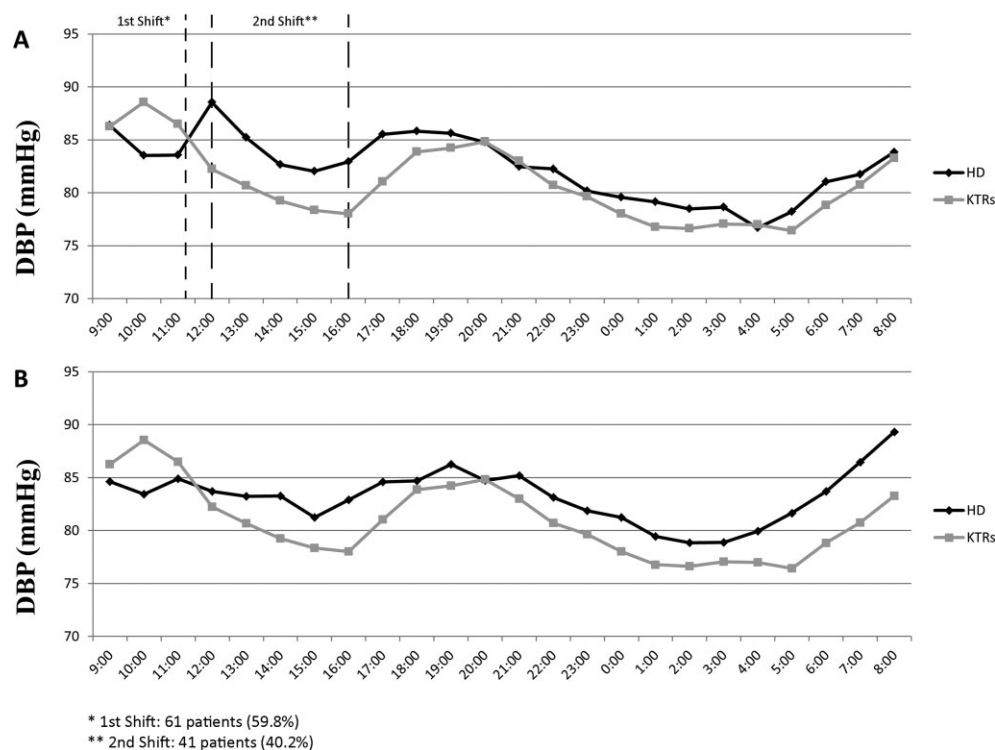


FIGURE 2: Trajectories of hourly mean DBP levels from 09.00 am to 08.59 am during a 24-h recording in KTRs and the (A) first and (B) second 24-h periods of a 48-h monitoring in patients undergoing HD.

in the Supplementary data, indicating in general a significant effect of time but significant between-group differences over only a few time-points during the second 24 h.

BPV indices in KTRs and HD patients

BPV indices of 24-h ambulatory BP recordings in KTRs and of dialysis-on and dialysis-off 24-h periods in HD patients are presented in Table 4. SBP-wSD and SBP-ARV were significantly lower in KTRs (SBP-ARV: 9.6 ± 2.3 mmHg) compared with either the first 24 h (SBP-ARV: 10.3 ± 3.0 mmHg; $P = 0.032$) or the second 24 h (SBP-ARV: 11.5 ± 3.0 mmHg; $P < 0.001$) of HD patients. With regard to DBP, wSD and ARV were again significantly lower in KTRs compared with HD patients (Table 4).

Dipping pattern

Supplementary, Table S2 presents the dipping patterns of SBP (reverse dipper, non-dipper, dipper, extreme dipper) in KTRs and HD patients over the first and second 24-h periods. While no significant differences were revealed, a marginally significant higher proportion of patients undergoing HD were found to be reverse dippers during the second 24-h period (KTRs: 29.4%; first 24-h HD: 29.4%; second 24-h HD: 38.2%; P -value versus second 24 h = 0.055).

DISCUSSION

This is the first study comparing the BP profile and short-term BPV indices between KTRs and those undergoing HD. We found that during all periods studied, KTRs had significantly lower 24 h, daytime and nighttime SBP and PP levels compared with HD

patients. DBP levels were numerically lower in KTRs, but no significant differences were found between the two study groups, with the exception of the second nighttime. A two-way ANOVA for repeated measurements showed a significant effect of RRT modality and time on ambulatory SBP during all periods studied, as well as a significant interaction between them. Notably, pair-wise comparisons revealed significantly higher estimated mean SBP levels on most occasions in patients under HD than in KTRs, with the highest difference between them observed at the end of the second 24 h, corresponding to the end of the interdialytic interval and the maximum volume overload for the HD group. Visual inspection of trajectories of ambulatory BP levels confirmed these results across different time-points in the first and second 24-h periods. PP followed a similar pattern to SBP with steady differences between groups over all periods studied; trajectories of DBP showed smaller differences between groups, especially over the first 24-h period. Short-term systolic and diastolic BPV indices were significantly lower in KTRs than in HD patients during all periods studied. The dipping profile was similar between the KTRs and HD patients over the first 24-h period, with a marginally higher proportion of HD patients being reverse dippers over the second nighttime.

Kidney transplantation has long been considered the optimal therapy for patients with ESKD due to greatly improved cardiovascular morbidity and mortality compared with dialysis [25]. However, the majority of KTRs still suffer from hypertension and have increased cardiovascular risk compared with the general population [3]. In relevant studies, the prevalence of hypertension in KTRs on the basis of office readings has been reported in up to 72% of patients [14, 26] using the 140/90 mmHg threshold, and up to 95% of them with the 130/80 mmHg threshold [13, 27]. The optimal office BP threshold for the diagnosis of

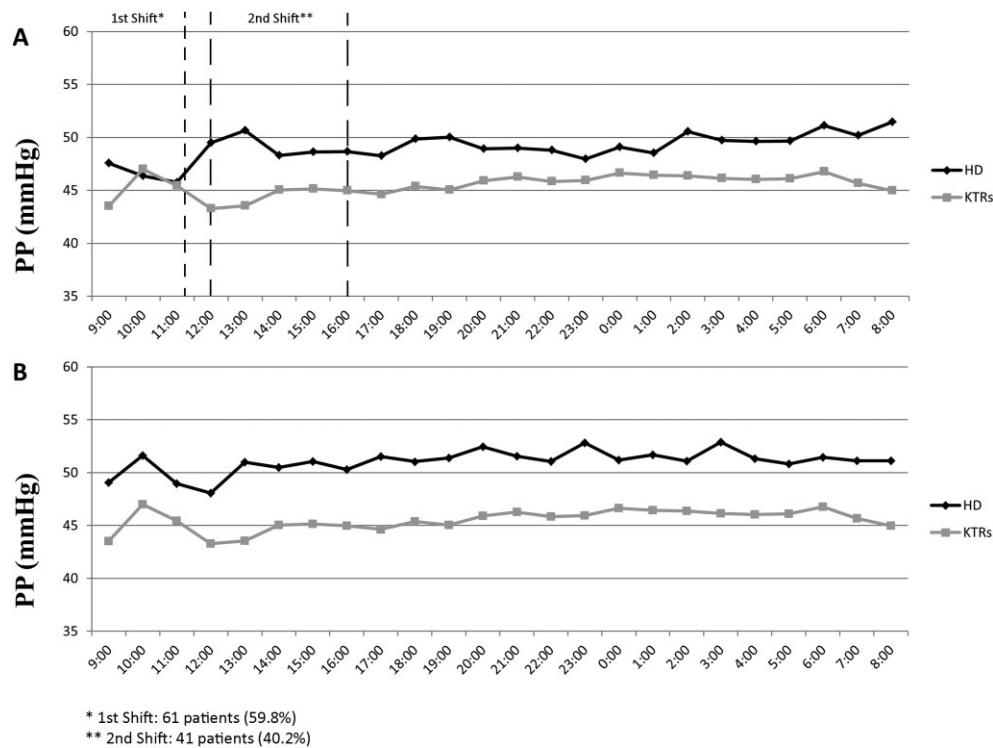


FIGURE 3: Trajectories of hourly mean PP levels from 09.00 am to 08.59 am during a 24-h recording in KTRs and the (A) first and (B) second 24-h periods of a 48-h monitoring in patients undergoing HD.

hypertension and the relevant BP treatment target in patients with CKD is still a matter of debate [9–11, 28, 29]. For patients with transplantation, there is no quality evidence that could be obtained from studies conducted in this field. However, both the 2017 American College of Cardiology/American Heart Association (ACC/AHA) BP guidelines [9] and the recent 2021 Kidney Disease: Improving Global Outcomes (KDIGO) BP guidelines [11] suggest a diagnosis threshold and a treatment target at 130/80 mmHg for KTRs. All guideline documents also advocate more extended use of ABPM in patients with CKD for several reasons [9–12]. In KTRs, several recent studies clearly supported this argument, providing evidence of a severe discordance of office BP readings in ABPM with regard to prevalence and control rates of hypertension at any given threshold [16], an extremely high prevalence (35–40%) of masked hypertension [13, 14, 16], as well as much stronger associations of ambulatory BP with renal function decline and cardiovascular target-organ damage [17].

As of this writing, there had been scarce preliminary data from rather small studies, comparing mean ambulatory BP values between KTRs and those undergoing HD. Goldsmith et al. [19] did not observe any significant differences in ambulatory BP levels between 25 patients undergoing a conventional HD program (12 h/week), 29 patients undergoing PD and 28 KTRs, in contrast to our findings; furthermore, significantly lower 24-h BP levels compared with all other groups were noted in 35 HD patients following a strategy of long dialysis sessions (24 h/week). Czyzewski et al. [18], by using of 44-h recordings in the HD group, found numerically higher but not significantly different 24-h, daytime and nighttime SBP levels in 50 KTRs 3 months post-transplantation compared with either 30 patients under PD or 40 patients under HD. Notably, 24-h DBP levels were significantly higher in KTRs compared with HD patients (first

20 h) at 3 months post-transplantation but not at 12 months, and significantly higher than in those under PD on both occasions. Our findings are in direct contrast to the above observations. First, we observed that KTRs have significantly lower SBP and PP levels than HD patients during all periods studied, and a similar DBP with the exception of the second nighttime. Second, through an elaborate analysis, we were able to confirm that these differences extend to ambulatory BP trajectories over the recording period. The differences between our findings and previous observations may be due to the much larger sample and careful design, including matching of KTRs and HD patients. They can also relate to the large time difference (10 and 20 years) [18, 19] from previous efforts; as considerable emphasis on hypertension and its consequences in KTRs has been given in previous years [4], better control rates could have been achieved in organized transplantation centres. Our study did not include patients under PD; however, we can hypothesize that KTRs should also have a lower SBP than PD patients, as in this largest study conducted to date comparing ambulatory BP profile in HD and PD patients, we found no significant differences in ambulatory BP levels and profiles between these groups, but with a numerically higher BP in PD patients [23].

This is the first study to assess short-term BPV indices in KTRs, showing significantly lower BP fluctuations over the 24-h period in KTRs compared with HD patients. We assessed BPV with modern indices and not SD and coefficient of variation, which are highly influenced by the mean and the weight of BP fall during the nighttime. The wSD index removes the contribution of this nocturnal BP fall (i.e. an important concern for ESKD patients), by accounting for the duration of daytime and nighttime periods [30]. The ARV index removes the contribution of a low sampling frequency and is sensitive to the individual

Table 3. Pair-wise comparisons of the estimated marginal SBP means at each time-point between the 24-h ABPM in KTRs and the second 24-h period of 48-h ABPM in patients undergoing HD

Hour	Mean difference KTRs–HD (mmHg)	95% confidence interval	P-value
10.00 am	3.3	–5.2 to 11.7	0.448
11.00 am	–1.7	–9.0 to 5.5	0.637
12.00 pm	–6.0	–13.0 to 1.0	0.092
01.00 pm	–8.0	–14.8 to –1.3	0.021
02.00 pm	–10.0	–16.9 to –3.2	0.004
03.00 pm	–10.2	–16.7 to –3.8	0.002
04.00 pm	–12.4	–19.5 to –5.2	0.001
05.00 pm	–11.9	–20.0 to –3.9	0.004
06.00 pm	–5.9	–13.0 to 1.2	0.105
07.00 pm	–7.9	–15.7 to 0.0	0.049
08.00 pm	–7.7	–15.5 to 0.0	0.051
09.00 pm	–8.5	–16.2 to –0.8	0.031
10.00 pm	–11.7	–18.8 to –4.5	0.002
11.00 pm	–11.3	–18.9 to –3.8	0.004
00.00 pm	–9.5	–17.2 to –1.9	0.015
01.00 am	–11.2	–18.8 to –3.7	0.004
02.00 am	–10.2	–18.3 to –2.2	0.013
03.00 am	–7.5	–15.5 to 0.5	0.065
04.00 am	–10.1	–18.6 to –1.7	0.019
05.00 am	–11.4	–19.5 to –3.3	0.006
06.00 am	–4.9	–12.7 to 3.0	0.220
07.00 am	–7.8	–15.2 to –0.4	0.039
08.00 am	–13.9	–21.5 to –6.2	<0.001
09.00 am	–8.1	–16.0 to –0.3	0.042

P < 0.05 is considered statistically significant, indicated in bold.

Table 4. Short-term BPV indices are estimated from the 24-h ABPM of KTRs and the first and second 24-h periods of 48-h ABPM in patients undergoing HD

	KTRs (N = 204)	HD (first 24 h) (N = 102)	P-value (KTRs versus first 24-h HD)	HD (second 24 h) (N = 102)	P-value (KTRs versus second 24-h HD)
24-h SBP wSD (mmHg)	12.5 ± 3.3	13.9 ± 4.2	0.005	14.3 ± 3.5	<0.001
24-h SBP ARV (mmHg)	9.6 ± 2.3	10.3 ± 3.0	0.032	11.5 ± 3.0	<0.001
24-h DBP wSD (mmHg)	9.7 ± 2.1	10.4 ± 2.5	0.018	10.4 ± 2.2	0.008
24-h DBP ARV (mmHg)	7.6 ± 1.7	8.4 ± 2.0	<0.001	9.1 ± 2.1	<0.001

Data are presented as mean ± SD.

P < 0.05 is considered statistically significant, indicated in bold.

order of consecutive BP measurements and therefore better captures intermittent BP fluctuations, all of which may account for its higher prognostic value compared with SD [31]. The short-term BPV has been previously studied only in 73 hypertensive KTRs through the ARV index, where a negative correlation between the percentage of flow-mediated dilatation and 24-h systolic ARV was shown [32]. One could hypothesize that the absence of intermittent volume removal inherent in the HD procedure may be the major factor for a decrease in short-term BPV in KTRs; however, in our aforementioned study comparing HD and PD patients, no differences were observed in short-term BPV [23]. Thus, other factors, including lower BP levels and improved responses of all the regulatory mechanisms involved in short-term adaptations of the cardiovascular system in everyday activities, may be involved in this improved BPV in KTRs. Concerning diurnal BP variations, no differences could be found in dipping patterns between the two study groups with the exception of a marginally higher proportion of reverse dippers in the HD group compared with KTRs during the second nighttime. No significant differences in dipping patterns were

observed between KTRs, HD and PD patients in the two previous relevant studies in the field [18, 19]. Of note, Covic et al. [33], who studied by ABPM 20 living KTRs 1 month before transplantation, and 1 month and 1 year after transplantation, reported that all patients were non-dippers 1 month after engraftment, while 15% were dippers before surgery, a finding that was associated with the dosage of calcineurin inhibitors. However, 1 year later, normal circadian rhythm was restored in 40% of KTRs.

Our study has its own strengths and limitations. To our knowledge, this is by far the largest study comparing ambulatory BP levels between KTRs and HD patients and the first to comparatively examine ambulatory BP trajectories across time. To do this, we employed a careful matching of KTRs and HD patients as well as an elaborate analysis, using a two-way ANOVA for repeated measurements to evaluate the effect of time and RRT type on BP levels and to investigate the presence of an interaction between them. This is also the first study to evaluate parameters of short-term BPV in KTRs, including modern and valid indices, as discussed above. All these parameters in KTRs were examined in separate comparisons of the dialysis-on

and the dialysis-off days, as previous studies have established significant differences between these days in BP regulation in HD patients [22–24]. The main limitation of our study is its observational nature; this is a common limitation of all studies comparing KTRs with HD patients, as conducting a randomized controlled trial assigning individuals in these modalities is not feasible. The study included participants from two large university departments and affiliated dialysis units; however, the actual physicians involved in the routine care of the studied patients were not sensitized to hypertension management beyond what is expected from an average nephrologist, and, thus, our findings can be considered representative of the routine practice in Greece and other European regions. Another limitation could be that our study included patients of Caucasian origin only, and, thus, whether our findings are valid for other racial/ethnic groups needs further investigation.

In conclusion, this study showed that ambulatory SBP and PP levels were lower in KTRs than in patients undergoing HD during all periods studied, whereas a significant difference in DBP was noted only during the second nighttime, corresponding to the end of the interdialytic interval. A two-way ANOVA for repeated measurements showed a significant effect of RRT modality and time on ambulatory SBP and PP during all periods studied, as well as a significant interaction between them. BPV indices were also found to be significantly lower in KTRs than in HD patients. The dipping profile did not differ between the two study groups, again with a marginal difference over the second nighttime. These results suggest that KTRs have a more favourable ambulatory BP profile compared with HD patients, in contrast to previous observations. Future studies are needed to examine longitudinal associations of office and ambulatory BP with hard renal and cardiovascular outcomes in KTRs, in order to fully define the hypertension-associated risks and the optimal targets for treatment.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

ACKNOWLEDGEMENTS

The authors wish to thank the doctors and nurses of participating centres involved in everyday patient care and the study participants for volunteering for the study.

FUNDING

This paper was not supported by any source and represents an original effort of the authors.

CONFLICT OF INTEREST STATEMENT

The authors wish to state that they do not have any conflict of interest to disclose regarding this paper.

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