

## ORIGINAL RESEARCH

# Sleep-Disordered Breathing and 24-Hour Ambulatory Blood Pressure Monitoring in Renal Transplant Patients: Longitudinal Study

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**BACKGROUND:** Sleep-disordered breathing (SDB) is considered a strong risk factor for hypertension in the general population. This disturbance is common in end-stage kidney disease patients on long-term hemodialysis and improves early on after renal transplantation. Whether SDB may be a risk factor for hypertension in renal transplant patients is unclear.

**METHODS AND RESULTS:** We investigated the long-term evolution of simultaneous polysomnographic and 24-hour ambulatory blood pressure (BP) monitoring recordings in a cohort of 221 renal transplant patients. Overall, 404 paired recordings were made over a median follow-up of 35 months. A longitudinal data analysis was performed by the mixed linear model. The apnea-hypopnea index increased from a median baseline value of 1.8 (interquartile range, 0.6–5.0) to a median final value of 3.6 (interquartile range, 1.7–10.4;  $P=0.009$ ). Repeated categorical measurements of the apnea-hypopnea index were directly associated with simultaneous 24-hour, daytime, and nighttime systolic ambulatory BP monitoring (adjusted analyses;  $P$  ranging from 0.002–0.01). In a sensitivity analysis restricted to 139 patients with at least 2 visits, 24-hour, daytime, and nighttime systolic BP significantly increased across visits ( $P<0.05$ ) in patients with worsening SDB ( $n=40$ ), whereas the same BP metrics did not change in patients ( $n=99$ ) with stable apnea-hypopnea index.

**CONCLUSIONS:** In renal transplant patients, worsening SDB associates with a parallel increase in average 24-hour, daytime, and nighttime systolic BP. These data are compatible with the hypothesis that the link between SDB and hypertension is causal in nature. Clinical trials are, however, needed to definitively test this hypothesis.

**Key Words:** 24-hour ambulatory blood pressure ■ chronic kidney disease ■ hypertension ■ renal transplantation ■ sleep apnea

Hypertension is a frequent condition in renal transplant patients and is strongly associated with the risk of cardiovascular complications and chronic graft dysfunction in this population.<sup>1</sup> In studies on office blood pressure (BP) monitoring, performed between 1993 and 2004,<sup>2–5</sup> the prevalence of this condition in renal transplant patients ranged from 45% to 86%, and from 17% to 61% in more recent studies.<sup>6–8</sup> In 2 surveys based on 24-hour ambulatory BP monitoring (ABPM),<sup>6,7</sup> approximately a quarter of the renal

transplant patients were classified as hypertensive, and nocturnal hypertension was prevalent in 71%<sup>6</sup> and 75%.<sup>7</sup> Risk factors for hypertension in transplant patients include donor-dependent factors (ie, a kidney graft coming from a deceased donor with hypertension and recipient-dependent factors, such as the presence of native kidneys), the use of calcineurin inhibitors and steroids, overweight and obesity, renal artery stenosis, chronic allograft dysfunction, and low glomerular filtration rate (GFR).<sup>1,9</sup> In the general population,

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## CLINICAL PERSPECTIVE

### What Is New?

- In patients with end-stage kidney disease on long-term dialysis, the apnea-hypopnea index (a biomarker of sleep-disordered breathing) substantially improves early on after renal transplantation, but it gradually worsens thereafter.
- In this study, worsening of the apnea-hypopnea index over time in renal transplant patients is associated with a parallel increase in average 24-hour, daytime, and nighttime systolic blood pressure, and this association was largely independent of ongoing changes in other risk factors.

### What Are the Clinical Implications?

- In renal transplant patients, the longitudinal association between ambulatory blood pressure measurements and the worsening of the apnea-hypopnea index is compatible with the hypothesis that sleep-disordered breathing is a causal risk for hypertension in these patients.
- Clinical trials are needed to test this hypothesis.

## Nonstandard Abbreviations and Acronyms

<b>ABPM</b>	ambulatory blood pressure
<b>AHI</b>	apnea-hypopnea index
<b>BMI</b>	body mass index
<b>BP</b>	blood pressure
<b>eGFR</b>	estimated glomerular filtration rate
<b>GFR</b>	glomerular filtration rate
<b>IQR</b>	interquartile range
<b>LMM</b>	linear mixed model
<b>SDB</b>	sleep-disordered breathing

sleep-disordered breathing (SDB) closely associates with hypertension,<sup>10</sup> particularly with nondipping and nocturnal hypertension,<sup>11</sup> but it is not recognized as a risk factor for hypertension in renal transplant patients. The lack of focus on SDB in the cause of hypertension in the transplant population probably depends on the fact that SDB regresses in most patients early on after transplantation,<sup>12–18</sup> taking it for granted that such an early improvement stabilizes thereafter.

In a recent longitudinal study,<sup>19</sup> we observed that SDB gradually reemerges in transplant patients. After a median follow-up of 3 years, ≈20% of these patients have moderate to severe SDB. In a comprehensive meta-analysis including >50 000 subjects from the general population,<sup>10</sup> mild, moderate, and severe SDB was associated with hypertension severity in a

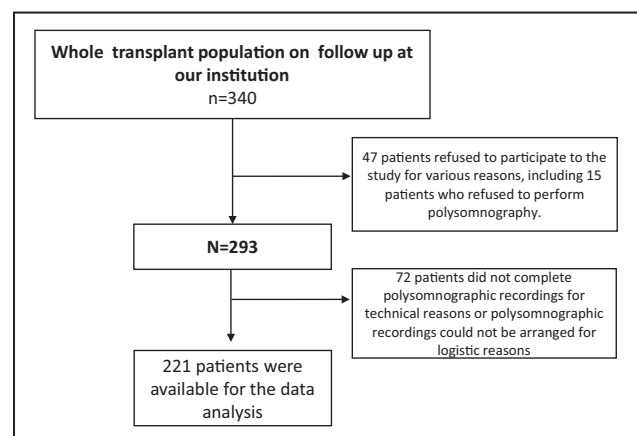
dose-response manner. Information on SDB as risk factor for hypertension in renal transplant patients is limited. To the best of our knowledge, there is only 1 cross-sectional study in a group of 100 transplant patients examining the relationship between sleep apnea and routinely measured office BP.<sup>20</sup> Studies based on 24-hour ABPM and studies with a longitudinal design are both lacking. One of the aims of our above-mentioned longitudinal study<sup>19</sup> was to investigate the relationship between SDB and the golden standard of BP measurement, 24-hour ABPM, in renal transplant patients. Herein, we describe the longitudinal relationship between the BP metrics derived from 24-hour ABPM and the polysomnographic parameters in the same cohort of renal transplant patients.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The protocol was in conformity with the local ethical guidelines of our institution and with the Declaration of Helsinki. Informed consent was obtained from each participant.

## Patients

The study cohort was performed from March 2004 to June 2015 and included 221 renal transplant patients on follow-up at the nephrology, dialysis, and transplantation unit of Reggio Calabria, Italy. The flowchart of this cohort is shown in Figure 1. The baseline study was performed once patients had achieved a stable condition after renal transplantation, which was always at least 4 months after kidney grafting. The median duration of follow-up after the baseline study was 35 months (whole range, 8–110 months; interquartile range [IQR], 24–46 months).



**Figure 1.** Flowchart of the study cohort.

## Polysomnography

Polysomnographic studies were performed in the nephrology ward with patients sleeping in a quiet single bedroom or in a double room provided that the roommates were in a stable condition and did not need night care.<sup>12</sup> The polysomnography study consisted of continuous polygraphic, cardiorespiratory recording (by MEDATEC, Pamela Sleep Recorder, Medigas, Milan, Italy; or by the Somté recorder by Compumedics, Victoria, Australia) from surface leads for electromyography and from noninvasive sensors for nasal airflow, thoracic and abdominal respiratory effort, and oxyhemoglobin level (finger-pulse oxymeter). The transducers and lead wires allowed normal positional changes during sleep. Bedtime and awakening times were at each patient's discretion; the polysomnography was terminated after final awakening. Polysomnography records were made for sleep, breathing, oxygenation, and movements in 30-second periods. Abnormal breathing during sleep was defined as a complete cessation of air flow lasting  $\geq 10$  seconds (apnea) or a discernible reduction in respiratory airflow accompanied by a sustained decrease in oxyhemoglobin saturation (hypopnea). The average number of episodes of apnea and hypopnea per hour of sleep (the apnea-hypopnea index [AHI]) was calculated as the summary measure of SDB. For the categorical analysis, we used the AHI cut-off points adopted in the Wisconsin study<sup>21</sup>: 0 to  $< 5$  apnea-hypopnea episodes (normal sleep pattern),  $\geq 5$  to  $< 15$  episodes (mild SDB), and  $\geq 15$  episodes (moderate to severe SDB). Nocturnal hypoxemia was measured by considering the minimal and average  $O_2$  saturation as well as the number of  $O_2$  desaturation episodes during nighttime. A decrease in oxygen saturation was considered significant if the oxygen desaturation during the episode was  $\geq 4\%$  of the surrounding values. Nocturnal apneas were further classified according to the recommendations of the American Academy of Sleep Medicine Task Force.<sup>22</sup> Briefly, an apnea episode was classified as "central" when it was associated with a decrease in inspiratory muscle activity following an exhalation and as "obstructive" when inspiratory muscle activity was present without airflow. All recordings were analyzed by an observer blinded to the scope of the study.

Polysomnography was performed at baseline and repeated at 1- to 2-year intervals.

## Office BP and 24-Hour ABPM

Office BP is the average of 2 or 3 measurements at 1- to 2-minute intervals during the morning hours of the day of the polysomnographic and 24-hour ABPM recordings. BP measurements were done in sitting position by the attending physician or a nurse with

the cuff at heart level using sphygmomanometers, periodically tested and appropriately calibrated by the chief research technician of our research unit (R.T.). The 24-hour ABPM was performed using a device that conforms to the Association for the Advancement of Medical Instrumentation recommendations (Spacelabs 90207, Redmond, WA). Measurements were performed every 15 minutes both during the day (7 AM to 10 PM) and night (10 PM to 7 AM). Patients were instructed to maintain their usual level of activity. As an indicator of the BP burden during nighttime, we considered the average values of systolic and diastolic BP between 10 PM and 7 AM. Hypertension thresholds were defined according to the European Society of Hypertension recommendations: 24-hour average ABPM  $\geq 130/80$  mm Hg, daytime ABPM  $\geq 135/85$  mm Hg, and nighttime ABPM  $\geq 120/70$  mm Hg.<sup>23</sup> By protocol, 24-hour ABPM studies were always performed on the same day of the polysomnographic recordings and, as with these recordings, were done at baseline and repeated every 1 or 2 years.

## Laboratory Data

Laboratory data, either collected during the same day of the polysomnographic recording or during the visit preceding the same recording (in general within 2 weeks) were abstracted from electronic clinical files from our unit. Serum lipids, glucose, albumin, phosphate, parathyroid hormone, and hemoglobin levels were measured by standard methods in the routine clinical laboratory. hs-CRP (high-sensitivity C-reactive protein) was measured following the high-sensitivity method (Dade Behring, Marburg, Germany). Serum creatinine was measured by an automated technique, according to the Jaffe chromogen method (calibrated to the isotope dilution mass spectrometry standard) implemented in an autoanalyzer. The estimated GFR (eGFR) was estimated by the modification of diet in renal disease equation developed by Levey et al.<sup>24</sup>

## Statistical Analysis

Data are summarized as mean and SD, median and IQR, or percentage frequency, where appropriate. Comparisons among AHI categories were performed by linear trend analysis. Within-patient comparisons were performed by paired *t* test. The study had no missing data for the variables included in the multivariable models.

The relationships between repeated 24-hour ABPM values and simultaneous polysomnographic data (AHI, number of  $O_2$  desaturation episodes per hour, minimum  $O_2$  and average nocturnal  $O_2$  saturation) were analyzed by crude and multiple linear

**Table 1. Main Demographic, Clinical, and Biochemical Baseline Characteristics of Patients Grouped by Baseline AHI**

Baseline Values	Whole Group (n=221)	Baseline AHI, Episodes/h			P Value for Trend
		<5.0 (n=166)	≥5–<15 (n=37)	≥15 (n=18)	
Age, y	46.9±11.6	45.4±11.9	50.7±9.6	53.1±9.4	0.001
Organ from living donors, %	12.3	11.5	18.9	5.6	0.99
Male sex, %	70.1	65.7	89.2	72.2	0.065
Active smokers, %	10	10	10	14	0.70
Past smokers, %	41	38	48	50	0.23
Diabetes mellitus, %	9.0	7.8	8.1	22.2	0.097
Background cardiovascular complications, %	10.9	9.6	10.8	22.2	0.16
Sodium, mEq/L	140.0±4.7	139.9±4.9	140.2±4.9	140.7±2.5	0.51
Potassium, mEq/L	4.2±0.5	4.2±0.5	4.1±0.5	4.4±0.5	0.33
Cholesterol, mg/dL	180±36	180±37	177±33	182±37	0.96
HDL cholesterol, mg/dL	55±16	55±15	55±20	51±11	0.34
LDL cholesterol, mg/dL	100±34	102±36	92±27	104±33	0.64
BMI, kg/m <sup>2</sup>	25.9±3.6	25.4±3.3	27.2±4.0	28.1±4.0	<0.001
Hemoglobin, g/dL	13.0±1.6	12.9±1.7	13.3±1.4	12.6±2.0	0.998
Albumin, g/dL	4.2±0.4	4.2±0.4	4.1±0.4	4.1±0.3	0.18
Phosphate, mg/dL	3.3±0.8	3.3±0.8	3.2±0.7	3.7±0.8	0.16
PTH, pg/mL	67 (43–106)	67 (41–100)	64 (45–191)	70 (49–115)	0.72
hs-CRP, mg/L	1.47 (0.62–3.10)	1.43 (0.59–2.93)	1.20 (0.47–3.45)	2.43 (1.34–7.62)	0.58
eGFR-MDRD <sub>186</sub> , mL/min per 1.73 m <sup>2</sup>	56.1±20.5	55.9±21.0	56.3±18.5	57.7±20.6	0.10

Data are expressed as mean±SD, median (interquartile range), or percentage frequency, as appropriate. AHI indicates apnea-hypopnea index; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; and PTH, parathyroid hormone.

mixed models (LMMs),<sup>25</sup> including all factors that differed among AHI groups (Table 1), with  $P \leq 0.10$  at baseline. In these models, body mass index (BMI) and eGFR were introduced as repeated measurements and data were expressed as regression coefficients: 95% CIs and  $P$  values. Data analysis was performed by SPSS for Windows (version 24.0; SPSS Inc, Chicago, IL).

## RESULTS

During the period of enrollment (2004–2015), the total transplant population on follow-up at our institution consisted of 340 patients. A total of 47 patients refused to participate in the study, and 72 did not complete polysomnographic recordings for technical reasons or polysomnographic recordings could not be arranged for logistic reasons (Figure 1). Thus, the final study population included 221 renal transplant patients (Table 1). The mean age was 47±12 years, and 70% were men. Of the patients, 9% were diabetics. The causes of chronic kidney disease (retrospectively established from an analysis of clinical files) were as follows: glomerulonephritis in 82 cases (37%), diabetic kidney disease in 18 cases (8%), cystic kidney diseases in 20 cases (9%), interstitial nephropathy

in 13 cases (6%), congenital anomalies of the kidney and urinary tract in 10 cases (4%), hypertensive nephrosclerosis in 2 cases (1%), hereditary nephropathies in 2 cases (1%), acute kidney injury in 2 cases (1%), and other causes/unknown in the remaining 72 cases (33%). Most patients received the organ from cadaveric donors (88%), and a minority received the organ from living donors (12%). Most patients (71%) were on triple immunosuppressive therapy (3-drug combinations, among which were cyclosporine, steroids, azathioprine, tacrolimus, sirolimus, and mycophenolate), and the remaining patients were on double therapy (28%) or on monotherapy (1%) with these agents. Twenty-four patients had experienced cardiovascular events. In detail, 18 had experienced 1 event (myocardial infarction in 3, stroke in 4, transient ischemic attack in 3, angina in 2, arrhythmia in 4, and peripheral vascular disease in 2), and the other 6 had ≥2 of these events. Of the patients, 10% were active smokers and 41% were past smokers. In this cohort, no heavy drinker was included, according to the definition of the Substance Abuse and Mental Health Services Administration (ie, 8 drinks per week in women and 15 drinks per week in men). A total of 195 patients were on antihypertensive therapy. Sixty-seven patients were on monotherapy with



calcium channel blockers ( $n=12$ ),  $\beta$  blockers ( $n=25$ ), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers ( $n=24$ ), sympatholytic or vasodilatory agents ( $n=5$ ), and diuretics ( $n=1$ ). A total of 128 patients were on multiple therapy, taking various combinations of these drugs. Of the patients, 10% were being treated with erythropoietin-stimulating agents and 42% were being treated with statins. eGFR was, on average,  $56.1 \pm 20.5$  mL/min per  $1.73$  m<sup>2</sup> (range, 7.2–135.9 mL/min per  $1.73$  m<sup>2</sup>). As shown in Table 1, age, number of antihypertensive drugs, and BMI were progressively higher across AHI categories, denoting progressive SDB severity. Diabetes mellitus ( $P=0.097$ ) and male sex ( $P=0.065$ ) showed a weak tendency to associate with a higher AHI. The use of statins, steroids, and erythropoietin-stimulating agents did not associate with the AHI in the analyses adjusting for age and BMI ( $P$  ranging from 0.14–0.33).

### Baseline Polysomnographic and Office BP and ABPM Data

At baseline, the median value of the AHI was 1.8 episodes/h (IQR, 0.6–5.0 episodes/h). A total of 166 patients (75%) had an AHI <5 episodes/h, 37 patients (17%) had an AHI ranging from 5 to <15 episodes/h, and the remaining 18 patients (8%) had an AHI  $\geq 15$  episodes/h. As expected, the number of O<sub>2</sub> desaturation episodes and the average

and the minimum O<sub>2</sub> saturation worsened from the first to the third AHI stratum (Table 2). Baseline office BP was, on average,  $132 \pm 16/78 \pm 10$  mm Hg and did not differ across AHI strata (Table 2). At baseline, 105 patients were classified as hypertensive (47.5%) by the 24-hour ABPM criterion ( $\geq 130/80$  mm Hg). Of note, the prevalence of nocturnal hypertension ( $\geq 120/70$  mm Hg) was high ( $n=166$  [75.1%]) and by far exceeded daytime hypertension prevalence ( $\geq 135/85$  mm Hg) ( $n=63$  [28.5%]). As shown in Table 2, the mean values of baseline 24-hour, daytime, and nighttime systolic BP increased in close parallelism with the AHI. Furthermore, the average number of antihypertensive drugs increased across AHI strata (AHI <5 episodes/h,  $1.8 \pm 1.2$  antihypertensive drugs;  $\geq 5$  and <15 episodes/h,  $1.9 \pm 1.0$  antihypertensive drugs; and  $\geq 15$  episodes/h,  $2.4 \pm 1.1$  antihypertensive drugs) ( $P=0.046$ ) (Table 2). The BMI was progressively higher across AHI strata (Table 1) but was largely unrelated to ABPM parameters (24-hour systolic ABPM:  $r=0.10$ ,  $P=0.12$ ; daytime systolic BP:  $r=0.09$ ,  $P=0.17$ ; and nighttime systolic BP:  $r=0.10$ ,  $P=0.14$ ).

### Longitudinal Polysomnographic and ABPM Data

Over a median follow-up of 35 months (IQR, 24–46 months), 404 simultaneous polysomnographic and ABPM recordings were performed. The median AHI increased from a baseline median value of

**Table 2. Polysomnography, Office BP, and 24-Hour ABPM Data Across AHI Strata at Baseline**

Baseline Values	Whole Group (n=221)	Baseline AHI, Episodes/h			P Value for Linear Trend
		<5.0 (n=166)	$\geq 5$ –<15 (n=37)	$\geq 15$ (n=18)	
Polysomnographic data					
AHI, episodes/h	1.8 (0.6–4.9)	1.1 (0.5–2.2)	7.5 (5.9–9.9)	28.5 (19.5–51.2)	<0.001
No. of O <sub>2</sub> desaturation episodes, episodes/h	1.30 (0.30–4.45)	0.70 (0.18–2.23)	5.6 (2.5–8.6)	18.6 (11.0–43.7)	<0.001
Minimum O <sub>2</sub> saturation, minimum SaO <sub>2</sub> , %	89 (86–92)	90 (88–93)	86.3 (80.5–88.5)	80.0 (70.5–88.0)	<0.001
Average O <sub>2</sub> saturation, mean SaO <sub>2</sub> , %	95.6 (94.1–96.4)	96.0 (94.7–96.6)	94.6 (93.5–95.9)	93.7 (90.5–95.6)	<0.001
Office BP					
Systolic BP, mm Hg	132 $\pm$ 16	132 $\pm$ 15	134 $\pm$ 15	136 $\pm$ 23	0.24
Diastolic BP, mm Hg	78 $\pm$ 10	78 $\pm$ 10	78 $\pm$ 10	79 $\pm$ 9	0.69
24-h ABPM					
24-h Systolic BP, mm Hg	125 $\pm$ 12	124 $\pm$ 12	126 $\pm$ 11	131 $\pm$ 16	0.03
24-h Diastolic BP, mm Hg	77 $\pm$ 8	76 $\pm$ 8	77 $\pm$ 8	80 $\pm$ 10	0.07
Daytime systolic BP, mm Hg	126 $\pm$ 12	125 $\pm$ 12	127 $\pm$ 10	131 $\pm$ 16	0.05
Daytime diastolic BP, mm Hg	78 $\pm$ 8	78 $\pm$ 8	79 $\pm$ 8	80 $\pm$ 10	0.12
Nighttime systolic BP, mm Hg	123 $\pm$ 13	122 $\pm$ 13	124 $\pm$ 13	130 $\pm$ 18	0.01
Nighttime diastolic BP, mm Hg	74 $\pm$ 9	73 $\pm$ 9	74 $\pm$ 8	79 $\pm$ 11	0.03
Antihypertensive treatment					
No. of antihypertensive drugs	2 (1–3)	2 (1–3)	2 (1–3)	2 (2–3)	0.08

Data are expressed as mean $\pm$ SD or median (interquartile range), as appropriate. ABPM indicates ambulatory BP monitoring; AHI, apnea-hypopnea index; BP, blood pressure; and SaO<sub>2</sub>, Oxygen Saturation.

1.8 episodes/h (IQR, 0.6–5.0) to 2.9 episodes/h (IQR, 1.0–6.6) at the second visit (time spanning from baseline: median, 32.2 months; IQR, 32.2–41.0 months) and to 3.6 episodes/h (IQR, 1.7–10.4) at the third visit (time spanning from baseline: median, 52 months; IQR, 36.8–67.3 months) ( $P=0.009$ ). The time trend of minimal nocturnal  $O_2$  saturation mirrored the AHI trend (first visit,  $87\pm 7\%$ ; second visit,  $87\pm 7\%$ ; third visit,  $85\pm 11\%$  [ $P=0.048$ ]).

The longitudinal relationships between repeated measurements of AHI and concomitant 24-hour,

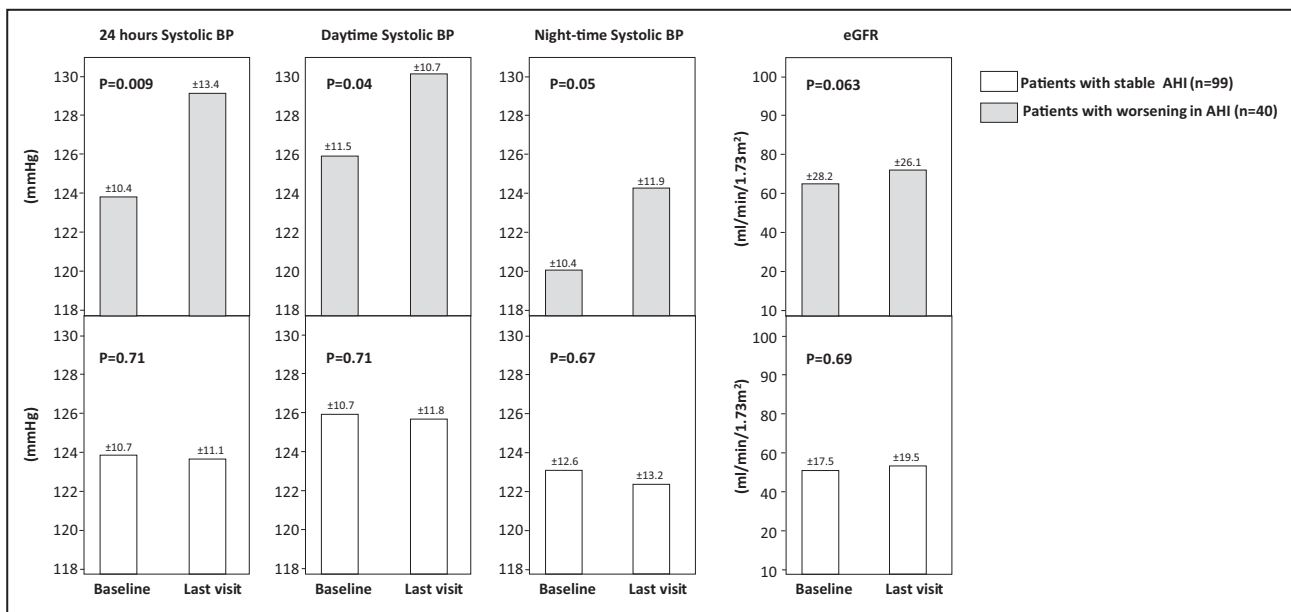
daytime, and nighttime systolic BP values over time were investigated in the entire study population (221 patients and 404 total observations) by LMMs. This analysis included 82 patients with a baseline visit only, 139 patients with at least 2 visits, and 44 patients with 3 visits. In unadjusted LMM analyses, repeated measurements of 24-hour, daytime, and nighttime systolic ABPM were directly related to categorically defined, repeated measurements of AHI ( $P$  ranging from 0.001–0.006) (Table 3, crude models). These relationships also did

**Table 3. LMM Analyses of Repeated Measurements of 24-Hour, Daytime, and Nighttime Systolic BP Over Time**

Factor	Dependent Variable: Repeated 24-h Systolic BP Measurements	
	Crude Model, Regression Coefficient (95% CI), $P$ Value	Adjusted Model, Regression Coefficient (95% CI), $P$ Value*
AHI, episodes/h		
<5	Reference	Reference
$\geq 5$ –<15	2.5 (–0.2 to 5.3), $P=0.069$	2.2 (–0.6 to 5.0), $P=0.12$
>15	5.3 (1.5 to 9.0), $P=0.006$	5.0 (1.2 to 8.8), $P=0.01$
Age, y	...	0.004 (–0.12 to 0.13), $P=0.95$
Male sex	...	3.52 (0.46 to 6.6), $P=0.02$
Diabetes mellitus	...	4.86 (–0.22 to 9.74), $P=0.051$
BMI, kg/m <sup>2</sup>	...	0.06 (–0.30 to 0.41), $P=0.76$
eGFR, mL/min per 1.73 m <sup>2</sup>	...	–0.73 (–0.13 to –0.014), $P=0.016$
Factor	Dependent Variable: Repeated Daytime Systolic BP Measurements	
	Crude Model, Regression Coefficient (95% CI), $P$ Value	Adjusted Model, Regression Coefficient (95% CI), $P$ Value*
AHI, episodes/h		
<5	Reference	Reference
$\geq 5$ –<15	2.1 (–0.5 to 4.8), $P=0.11$	1.8 (–0.9 to 4.6), $P=0.19$
>15	5.5 (2.0 to 9.0), $P=0.002$	5.1 (1.5 to 8.7), $P=0.006$
Age, y	...	–0.032 (–0.15 to 0.089), $P=0.61$
Male sex	...	3.79 (0.85 to 6.74), $P=0.01$
Diabetes mellitus	...	3.72 (–0.97 to 8.41), $P=0.12$
BMI, kg/m <sup>2</sup>	...	0.09 (–0.26 to 0.43), $P=0.62$
eGFR, mL/min per 1.73 m <sup>2</sup>	...	0.05 (–0.11 to 0.005), $P=0.07$
Factor	Dependent Variable: Repeated Nighttime Systolic BP Measurements	
	Crude Model, Regression Coefficient (95% CI), $P$ Value	Adjusted Model, Regression Coefficient (95% CI), $P$ Value*
AHI, episodes/h		
<5	Reference	Reference
$\geq 5$ –<15	2.1 (–0.8 to 4.9), $P=0.15$	1.8 (–1.1 to 4.7), $P=0.23$
>15	6.6 (2.8 to 10.5), $P=0.001$	6.2 (2.3 to 10.1), $P=0.002$
Age, y	...	0.07 (–0.06 to 0.22), $P=0.28$
Male sex	...	1.90 (–1.54 to 5.35), $P=0.28$
Diabetes mellitus	...	6.2 (0.7 to 11.7), $P=0.027$
BMI, kg/m <sup>2</sup>	...	0.01 (–0.38 to 0.40), $P=0.96$
eGFR, mL/min per 1.73 m <sup>2</sup>	...	–0.09 (–0.16 to –0.02), $P=0.007$

AHI indicates apnea-hypopnea index; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; and LMM, linear mixed model.

\*Adjusted for age, sex, diabetes mellitus, BMI (repeated), and eGFR (repeated). Further adjustment for the type of polysomnographic recorder did not materially affect the relationship between repeated 24-hour systolic BP ( $P=0.02$ ) or daytime ( $P=0.015$ ) or nighttime ( $P=0.004$ ) systolic BP and the risk for AHI >15.



**Figure 2. Sensitivity analysis in 139 patients who had at least 2 simultaneous polysomnographic and 24-hour ambulatory blood pressure monitoring (ABPM) studies.**

Changes in 24-hour, daytime, and nighttime systolic blood pressure (BP) in patients who had worsening sleep-disordered breathing (SDB) from the first to the third study visit (ie, moved to an apnea-hypopnea index [AHI] category denoting a more severe degree of SDB) and in patients with stable AHI. No patient had improved SDB during follow-up. These analyses were performed in 139 patients who had at least 2 parallel polysomnographic and 24-hour ABPM recordings. eGFR indicates estimated glomerular filtration rate.

not materially change after data adjustment for potential confounders ( $P$  ranging from 0.002–0.01) (Table 3, adjusted models). In this model, the AHI was the sole variable that coherently associated with the 3 ABPM parameters (24-hour, daytime, and nighttime systolic BP). Similar to the baseline study, BMI was largely unrelated to the same parameters ( $P > 0.62$ ). The eGFR had robust associations with 24-hour and nighttime systolic BP, but the relationship between eGFR and nighttime systolic BP just failed to attain statistical significance ( $P = 0.07$ ).

In a sensitivity analysis restricted to the 139 patients with at least 2 longitudinal visits, 24-hour, daytime, and nighttime systolic BP significantly increased across visits ( $P \leq 0.05$ ) in patients with SDB worsening, defined as a transition from a lower to a higher AHI category ( $n = 40$ ), whereas the same BP metrics did not change ( $P$  ranging from 0.67–0.71) in patients ( $n = 99$ ) with stable AHI. The eGFR did not change significantly in either group (Figure 2).

In multiple LMM adjusting for potential confounders, repeated measurements of minimal nocturnal  $O_2$  saturation were significantly associated with simultaneous changes in nighttime systolic BP ( $P = 0.004$ ) but unrelated to concomitant changes in 24-hour ( $P = 0.17$ ) and daytime systolic BP values ( $P = 0.11$ ).

## DISCUSSION

In this longitudinal study, repeated measures of the AHI were directly associated with simultaneously

recorded 24-hour, daytime, and nighttime systolic BP. Furthermore, in a separate sensitivity analysis, the same 24-hour ABPM metrics all increased over time in patients with worsening SDB while remaining unchanged in patients with stable AHI. These associations were largely independent of potential confounders, such as age, sex, diabetes mellitus, BMI, and GFR. Overall, the results of this longitudinal study support the hypothesis that SDB is a risk factor for hypertension in renal transplant patients.

Hypertension is an established sequela of SDB in studies in the general population. A comprehensive meta-analysis by Hou et al documented that mild, moderate, and severe sleep apnea associates with hypertension in a dose-response manner as well as with a 2.8 higher risk for resistant hypertension.<sup>10</sup> Associations are population specific, and the putative link between SDB and hypertension should therefore be specifically confirmed in the target population, where such a link is suspected. As to the renal transplant population, until now, the relationship between SDB and hypertension has only been investigated by Molnar et al<sup>20</sup> in a cross-sectional study in renal transplant patients. Because of the limited evidentiary base that SDB is implicated in hypertension in these patients, neither a review from the 1980s<sup>26</sup> nor subsequent reviews conducted in 2011<sup>27</sup> and 2019<sup>28</sup> indicate SDB as a risk factor for hypertension in renal transplant patients. On the basis of evidence gathered in other conditions, a review by Weir et al, published in 2014,<sup>1</sup> did consider SDB to be a hypothetical risk

factor for hypertension posttransplantation. Yet, SDB is still not seen as a possible risk factor for hypertension in these patients in UpToDate, a periodically updated, evidence-based manual extensively used worldwide.<sup>9</sup>

Although the randomized trial remains the inescapable standard for the assessment of causality, follow-up and longitudinal studies provide useful information for the assessment of causality in observational settings.<sup>29</sup> Indeed, these studies provide information about individual changes in the variables of interest, exclude between-subject variation from error, and allow investigation of the relationship between predictor variables and relevant study end points. Follow-up<sup>30</sup> and longitudinal<sup>31</sup> analyses in the Wisconsin Sleep Study, a cohort study in the general population, coherently documented a relationship between a high AHI and incident hypertension independent of age, sex, BMI, waist circumference, and other risk factors. Likewise, in the present study, both in the cross-sectional analyses at baseline and in the longitudinal analyses, the relationship between AHI and ABPM parameters was largely independent of other risk factors, including BMI.

Sympathetic activity, which is markedly enhanced in transplant patients,<sup>32</sup> is considered to be the main mechanism by which SDB increases BP<sup>33</sup> in this population. In the hypothesis-generating study by Molnar et al, notwithstanding a more intensive use of antihypertensive drugs in patients with SDB compared with those without SDB, the systolic BP was  $\approx 8$  mm Hg higher in the former group, suggesting that the link between SDB and BP is fairly strong and of potential clinical relevance. Ours is the first longitudinal study testing this link in the transplant population. We adopted 24-hour ABPM as BP metric and performed 404 simultaneous polysomnographic and 24-hour ABPM recordings over a median follow-up of 3 years. We tested the relationship between these variables by the LMM,<sup>25</sup> an analytical approach that explicitly models individual change over time, is more flexible in terms of repeated measures, and does not require the same number of observations per subject, allowing time to be continuous rather than a fixed set of points. All these characteristics enable this model to analyze longitudinal data in studies performed in a clinical setting,<sup>25</sup> like in our study. Following this approach in unadjusted and adjusted analyses, we found that worsening SDB associates with a parallel increase in average 24-hour, daytime, and nighttime systolic BP, supporting the hypothesis that SDB is a risk factor for hypertension in the transplant population.

This study has limitations. First, it is observational in nature. Therefore, experimental studies are needed to definitively test the nature of the link between SDB and hypertension in renal transplant patients. Continuous positive airway pressure, the gold standard for the treatment of SDB, which lowers BP in patients with severe SDB and resistant hypertension,<sup>34</sup> as well as

interventions aimed at reducing body weight<sup>35</sup> and volume expansion<sup>36</sup> and other testable treatments can be considered.<sup>35</sup> Specific trials in transplant patients will prove or negate the hypothesis that SDB is causally linked to hypertension and the high cardiovascular risk in this population. Second, our population only included white patients, and our findings can therefore not be generalized to other ethnicities.

## ARTICLE INFORMATION

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