

## ORIGINAL ARTICLE

## Twenty four-hour ambulatory blood pressure profiles 12 months post living kidney donation

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### Introduction

Living kidney donors undergo a surgical procedure with no medical benefit to themselves, namely unilateral nephrectomy. A number of retrospective and cross-sectional studies adequately illustrate its acceptable level of safety [1–10]. An acute 50% loss of functional kidney mass however requires intense physiological adaptations that may, in susceptible individuals, predispose to blood pressure (BP) elevation, increased urinary protein excretion, or other metabolic abnormalities [11–15]. Thus, while it is safe for the vast majority of healthy individuals to undergo unilateral nephrectomy, the identification of donors destined to develop these abnormalities furthers the transparent nature of the transplant process. For

### Summary

Small blood pressure (BP) elevations may occur post kidney donation. This prospective study determined 24-h ambulatory BP (ABP) and other cardiovascular risk factor changes in 51 living donors over 12 months postdonation. Donors also provided 24-h urine collections for monitoring protein and creatinine clearance, 75 g oral glucose tolerance tests (OGTT), and fasting lipids. Nondipping was defined as night-day systolic (SBP) ratio  $\geq 0.9$ . Baseline and 12-month pre to postdonation comparisons were made both for dippers and nondippers. Of 51 donors, 35 were dippers and 16 nondippers. In these two groups, predonation 24-h SBP were  $115.2 \pm 8$  and  $115.6 \pm 10$  mmHg; serum creatinine (SCr)  $69.3 \pm 12$  and  $71.1 \pm 13$   $\mu\text{mol/l}$ ; and 24-h urine protein  $0.12 \pm 0.05$  and  $0.09 \pm 0.03$  g (all  $P = \text{NS}$ ) while at 12 months, 24-h SBP were  $111.4 \pm 11$  and  $114.3 \pm 8$  mmHg ( $P = 0.384$ ), SCr  $97.9 \pm 16$  and  $97.7 \pm 21$   $\mu\text{mol/l}$  ( $P = 0.810$ ); and 24-h urine protein  $0.139 \pm 0.09$  and  $0.111 \pm 0.07$  g/d ( $P = 0.360$ ) respectively. The 24-h SBP was significantly lower in the dippers at 12 months as compared with predonation ( $P = 0.036$ ). OGTT and lipid profiles remained normal in both groups. Predonation nocturnal nondipping does not carry adverse postdonation consequences over 12 months.

example, it is known that nocturnal nondipping based on 24-h ambulatory blood pressure (ABP) readings in some populations is associated with end-organ damage [16] even in the absence of hypertension [17,18]. We therefore hypothesized that the predonation 24-h ABP dipping profile of normotensive living kidney donors is predictive of their renal function and cardiovascular risk status at 12 months postdonation.

### Materials and methods

Our hospital is a university-affiliated tertiary care medical-surgical centre that currently performs approximately 100 renal transplants annually, of which about one-half are derived from living donors. The presurgical evaluation

for all living donors includes the exclusion of hypertension by office BP measurement ( $>140/90$  mmHg) and 24-h ABP monitoring ( $>135/85$  mmHg); renal insufficiency ( $<70$  ml/min/1.73 m<sup>2</sup>) by measurement of the 24-h urine-based creatinine clearance (CCr); proteinuria ( $>300$  mg/24 h); diabetes mellitus [fasting blood sugar (FBS)  $\geq 7.0$  mmol/l and 2-h BS  $\geq 11.1$  mmol/l on 75 g oral glucose tolerance testing (OGTT, Canadian Diabetes Association (CDA) 2003)]; and morbid obesity (BMI  $> 40$  kg/m<sup>2</sup>). In addition, nephrolithiasis and surgical contraindications to donation (e.g. multiple renal arteries) are excluded through abdominal computerized tomography. The standard postdonation evaluation includes a single office visit at 3 months postdonation, during which a sphygmomanometer-measured BP is obtained, renal function is assessed by estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [19], and a random urine sample is evaluated for proteinuria. All potential donors who received prior approval to donate by a team independent of the study investigators were subsequently approached for participation in this study.

Donors who provided informed consent for this prospective study were asked to repeat all of their predonation testing at 12 months postdonation, with the exception of radiographic imaging. The 24-h ABP measurements were performed using a calibrated DynaPulse 5000A<sup>®</sup> monitor (Pulse Metric, Vista, CA, USA). Awake and sleep times were self-reported and used to define the waking (daytime) and sleep (nighttime) periods. Nocturnal nondipping was defined as a nighttime-to-daytime SBP ratio  $\geq 0.9$ . An additional BP measurement by American Heart Association guidelines using a sphygmomanometer cuff was obtained at the time of the 24-h ABP measurement both pre and postdonation; this 'office' BP value was also used for data analysis.

Renal function was estimated by the serum creatinine (SCr) and CCr from a timed 24-h urine collection. All donors provided SCr measurements, 24-h urine collection for protein excretion and CCr, 75 g oral glucose tolerance testing (OGTT, CDA 2003), and fasting lipid profiles both predonation and at 12 months postdonation. Height and weight were used to estimate the BMI in kg/m<sup>2</sup>. Ethnicity was defined as white (European ancestry), black (African), East Asian (China, Japan, Korea, Thailand, Vietnam, Philippines), and South Asian (Indian subcontinent, including India, Pakistan, Bangladesh, Nepal, and Sri Lanka).

The *a priori* analyses performed included comparisons between predonation values and subsequent 12-month postdonation values for all parameters separately for donors classified as either dippers or nondippers based on their predonation 24-h ABP profile. The required sample size was estimated at a total of 48 patients in order to

provide a power of 80% and alpha 0.05 at detecting a systolic BP change of 5 mmHg with an underlying normotensive population assumption for an SD of 12 mmHg.

Pre to postdonation comparisons within and between the predonation dippers and nondipper groups were made by a paired or unpaired Student *t*-test, Wilcoxon rank sum test or chi-square analysis as appropriate. Bivariate comparisons were made using Pearson's correlation coefficient. A two-tailed *P*-value  $<0.05$  was considered statistically significant for all comparisons. SAS version 9.2 (Cary, NC, USA) was the statistical software package used. The study was approved by the Research Ethics Boards at both St. Michael's Hospital and the University of Toronto. Conduct of the study was in accordance with the Declaration of Helsinki.

## Results

### Donor pool and study population characteristics

Between October 1, 2004 and April 30, 2007 there were 129 renal transplants performed from live donors (70 from biologically related, 56 from emotionally related, two from paired exchange, and one from an anonymous nondirected donor). These donors constituted the eligible pool for the study. Sixty-nine (54%) patients provided initial consent for the study. Reasons for non provision of consent included unwillingness to travel to the transplant centre or provide other follow-up testing ( $n = 31$ ) foreign residence ( $n = 9$ ), or competing protocols ( $n = 9$ ). Eleven donors did not provide any specific reason for not consenting. Fifty-one (74%) consented donors completed their testing at 12 months postdonation. Their demographic characteristics are provided in Table 1. There were no significant differences noted in any predonation clinical parameters among those who completed the study and those who did not return for follow-up testing. All those who did not return reported themselves as healthy

**Table 1.** Demographic characteristics of study participants ( $n = 51$ ).

Age [mean $\pm$ SD, (range)]	46.5 $\pm$ 10 (26–69)
Gender (M/F)	11/40
Smoker (yes/no)	6/45
Ethnicity	
White	31
Black	3
East Asian	8
South Asian	7
other	2
Relation to recipient	
Parent	5
Sibling	9
Child	3
Spouse/partner	26
Friend	8

and in no need for medical follow-up. All organs were laparoscopically retrieved with no unusual vascular anatomy or subsequent surgical complications noted. Of the 51 donors, 35 were dippers and 16 were nondippers prior to donation.

### Changes in cardiovascular risk parameters

Changes in ABP, renal function, urine protein excretion, BMI, glucose levels, and lipid levels in both dippers and

nondippers, from predonation to 12 months postdonation are summarized in Table 2.

### Blood pressure

Changes in BP including office measurements and 24-h ABP-based daytime and nighttime measurements, the night-day SBP ratio, and heart rate for the study population are summarized in Table 2. At their predonation baseline, there were 36 dippers and 15 nondippers. The

**Table 2.** Change in 24-h ambulatory blood pressure, renal function, glucose tolerance, and lipid profiles from predonation to 12 months postdonation based on predonation dipping status\*.

Parameter	Dippers (n = 35)			Nondippers (n = 16)		
	Predonation	12 months postdonation	P-value	Predonation	12 months postdonation	P-value
Body mass index (kg/m <sup>2</sup> )	24.6 ± 3 (19–35)	24.6 ± 3 (19–32)	0.865	24.8 ± 5 (17–35)	25.6 ± 4 (19–33)	0.590
Office BP (mmHg)						
Systolic	119.0 ± 12 (90–146)	116.5 ± 16 (97–164)	0.113	118.5 ± 11 (100–140)	117.2 ± 12 (98–144)	1.000
Diastolic	75.2 ± 9 (50–88)	72.5 ± 9 (56–87)	0.217	71.5 ± 8 (60–88)	79.3 ± 10(61–102)	0.034
24-h ABP (mmHg)						
Systolic	115.2 ± 8 (104–141)	111.4 ± 11 (93–145)	0.036	115.6 ± 10 (96–130)	114.3 ± 8 (101–128)	0.762
Diastolic	71.0 ± 5(61–81)	69.3 ± 6 (53–85)	0.138	69.9 ± 6 (58–77)	70.1 ± 6 (60–81)	0.939
Daytime BP						
Systolic	122.4 ± 10 (109–151)	118.6 ± 16 (97–175)	0.026	117.2 ± 9 (97–131)	116.0 ± 8 (98–131)	0.678
Diastolic	75.5 ± 6 (64–87)	73.8 ± 7(54–87)	0.397	72.7 ± 6 (60–87)	72.2 ± 7 (62–81)	0.706
Nighttime BP						
Systolic	101.2 ± 8 (88–121)	99.4 ± 12 (79–131)	0.324	111.9 ± 11 (92–131)	108.6 ± 11 (86–128)	0.473
Diastolic	61.9 ± 8 (46–78)	61.0 ± 7 (47–75)	0.821	65.3 ± 7 (52–75)	65.3 ± 9 (52–83)	0.969
Night-day ratio						
Systolic	0.827 ± 0.05 (0.72–0.89)	0.845 ± 0.09 (0.55–1.01)	0.175	0.954 ± 0.04 (0.90–1.02)	0.936 ± 0.07 (0.77–1.06)	0.624
Diastolic	0.821 ± 0.10 (0.61–1.04)	0.829 ± 0.09 (0.63–1.00)	0.651	0.900 ± 0.08 (0.68–0.98)	0.906 ± 0.10 (0.74–1.07)	0.969
Heart rate (beats/min)						
24-h	73.4 ± 7 (59–90)	74.0 ± 9 (60–99)	0.925	71.7 ± 7 (62–84)	70.4 ± 8 (52–84)	0.865
Daytime	77.1 ± 8 (62–96)	79.1 ± 12 (62–122)	0.877	74.9 ± 8 (63–86)	75.8 ± 9 (54–90)	0.651
Nighttime	67.7 ± 8 (57–89)	66.6 ± 10 (54–99)	0.767	65.4 ± 8(53–80)	64.3 ± 7 (46–77)	0.895
Serum creatinine (μmol/l)	69.3 ± 12 (50–98)	97.9 ± 16 (73–150)	<0.0001	71.1 ± 13 (56–96)	97.7 ± 21 (73–150)	0.0006
24-h urine creatinine clearance (ml/min/1.73 m <sup>2</sup> )	109.9 ± 26 (77–163)	78.2 ± 16(50–113)	<0.0001	108.1 ± 20 (77–157)	59.4 ± 16(36–87)	<0.0001
24-h urine protein excretion (g/d)	0.119 ± 0.05 (0.06–0.28)	0.139 ± 0.09 (0.05–0.46)	0.603	0.090 ± 0.03 (0.03–0.13)	0.111 ± 0.07 (0.05–0.30)	0.866
Blood glucose (mmol/l)						
Fasting	4.98 ± 0.3 (4.4–5.9)	4.85 ± 0.4 (4.2–5.9)	0.154	5.29 ± 0.5 (4.4–6.2)	5.12 ± 0.5 (4.3–6.3)	0.273
2-h post 75 g oral glucose load	5.62 ± 0.9 (4.1–7.3)	5.32 ± 1.3(2.9–8.4)	0.174	5.46 ± 1.7 (3.6–10.2)	5.07 ± 1.1 (3.3–6.8)	0.710
Lipid profile (fasting)						
Total cholesterol	4.94 ± 0.9 (3.2–7.1)	5.03 ± 1.1 (3.6–8.1)	0.756	5.26 ± 0.9 (3.4–6.8)	5.44 ± 1.1 (3.6–7.4)	0.559
HDL cholesterol	1.48 ± 0.4 (0.7–2.5)	1.52 ± 0.5 (0.7–2.8)	0.834	1.49 ± 0.5 (0.7–3.0)	1.44 ± 0.5 (0.7–2.8)	0.910
LDL cholesterol	2.94 ± 0.9 (1.4–5.2)	2.95 ± 1.0 (1.3–5.3)	0.767	3.31 ± 0.8 (1.9–5.0)	3.34 ± 0.8 (2.2–5.0)	0.985
Triglycerides	1.02 ± 0.5 (0.3–2.0)	1.25 ± 0.7(0.4–3.2)	0.287	0.98 ± 0.4 (0.5–1.7)	1.46 ± 0.8 (0.6–3.2)	0.131
Haemoglobin (g/l)	135.4 ± 10 (120–166)	133.6 ± 11 (111–156)	0.500	135.0 ± 13 (113–164)	130.4 ± 15 (94–165)	0.505

ABP, ambulatory blood pressure.

\*All P-values refer to within-group comparisons. For between group comparisons please refer to text.

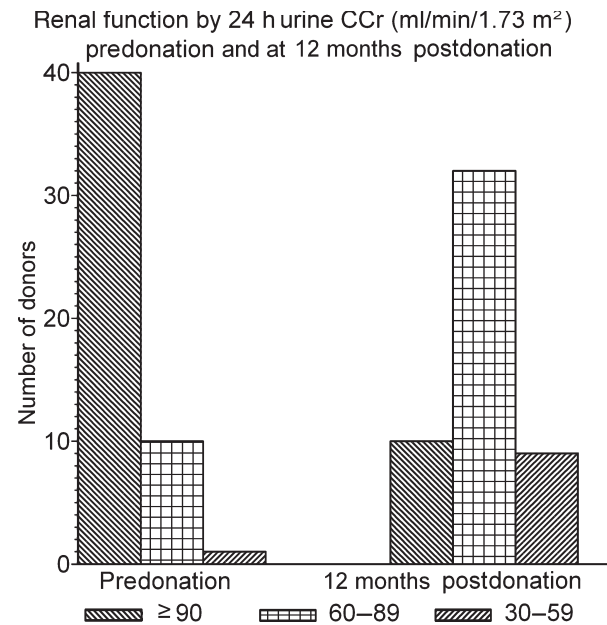
night-day SBP ratio was  $0.827 \pm 0.05$  (0.72–0.89) in the dippers and  $0.954 \pm 0.04$  (0.90–1.02) in the nondippers ( $P < 0.0001$ ). Other than the night-day SBP ratio, there were no statistically significant differences between predonation dippers and nondippers. At 12 months, there was maintenance of a statistically significant difference between predonation dippers and nondippers with respect to their night-day SBP ratio ( $P = 0.008$ ), but not systolic blood pressure (SBP) ( $P = 0.384$ ), or diastolic blood pressure (DBP) ( $P = 0.677$ ). Of note, the 24-h SBP was significantly lower in the dippers at 12 months as compared with predonation (Table 2). At 12 months, there were 31 dippers and 20 nondippers. Eight predonation dippers subsequently became nondippers while four nondippers subsequently became dippers. In the eight subjects who were previously dippers but who became nondippers after nephrectomy, there was no increase in blood pressure compared to the 28 donors who remained dippers (SBP  $112.7 \pm 9.3$  vs.  $111.0 \pm 12.4$  mmHg at 12 months,  $P = 0.723$ ). None of the 51 subjects met combined office- and 24-h ABP definitions for hypertension or required antihypertensive therapy at any time.

### Renal function and protein excretion

Change in renal function as assessed by the SCr level and 24-h urine collection is provided in Table 2. Renal function was significantly less at 12 months postdonation ( $P < 0.0001$  for each). There was no difference in 24-h urine creatinine content from pre to postdonation ( $11.4 \pm 4$  vs.  $10.3 \pm 3$  mmol/l,  $P = 0.27$ ). There was no correlation between the change in 24-h urine CCr and change in nocturnal fall in SBP ( $R = 0.142$ ,  $P = 0.373$ ). Donors are classified by their predonation and 12-month 24-h urine CCr in Fig. 1. Although a small number of donors reached a CCr between 30 and 59 ml/min/1.73 m<sup>2</sup>, none reached a lower CCr. In this subgroup of donors, SBP change was  $-4.6 \pm 7.2$  mmHg (range -10 to +16 mmHg) ( $P = \text{NS}$  versus others). No differences in 12-month renal function were noted between predonation dippers and nondippers ( $P = 0.810$ ). There was also no correlation between the change in 24-h urine CCr and change in BP ( $R = 0.011$ ,  $P = 0.950$ ). Likewise, no differences were detected in the 24-h urine protein excretion rate between dippers and nondippers ( $P = 0.360$ ).

### Other cardiovascular risk parameters

With respect to the other predonation cardiovascular risk parameters shown in Table 2, there was no change at 12 months in BMI; either fasting or 2-h blood glucose levels; fasting total cholesterol, HDL, LDL, or triglycerides; and haemoglobin in either dippers or nondippers.



**Figure 1** Renal function predonation and at 12 months postdonation as estimated by the 24-h urine collection for creatinine clearance.

No differences were noted between the dipper- or non-dipper subgroups at baseline or 12 months (Table 2,  $P = \text{NS}$  for all comparisons). No subjects required lipid-lowering therapy at any time.

Of note, 15 of the subjects were of either East or South Asian origin. Asian donors had a lower pre but not postdonation 24-h urine CCr compared to non-Asians ( $98.1 \pm 17$  vs.  $113.6 \pm 22$  ml/min/1.73 m<sup>2</sup>,  $P = 0.04$  and  $67.0 \pm 22$  vs.  $75.0 \pm 16$  ml/min/1.73 m<sup>2</sup>,  $P = 0.26$  respectively), while having a similar 24-h SBP level both pre and postdonation ( $109.1 \pm 6$  vs.  $113.2 \pm 9$  mmHg,  $P = 0.18$  and  $109.2 \pm 9$  vs.  $113.6 \pm 11$  mmHg,  $P = 0.19$ ). Ethnicity did not influence change in CCr or SBP in this group as compared with non-Asians ( $P = \text{NS}$  for each).

### Discussion

This prospective, observational study in kidney donors provides some reassurance of the short-term safety of unilateral nephrectomy in otherwise healthy individuals and extends previous observations [20]. The 24-h BP and daytime BP were lower in dippers after 12 months. Nocturnal nondipping present prior to donation did not carry any added postdonation risk. No increase in the night-day SBP ratio was noted. Postdonation renal function and protein excretion did not correlate with BP levels. There was also no change in any parameters associated with cardiovascular risk including BMI, fasting or postprandial glucose levels, fasting lipid profile with

the possible exception of triglycerides, and haemoglobin at 12 months postdonation.

A previous study of 15 donors performed between 2 weeks and 3 months postdonation has demonstrated that the night-day BP ratio is unchanged after nephrectomy. However, change in this ratio correlated with the decrease in CCr [14]. We were unable to corroborate this finding, likely because of the longer interval between the two ABP measurements and the use of outpatient, rather than inpatient readings. A substantial loss of renal function, to the extent of 70%, may be required before the appearance of an elevated BP [21]. This is not typically seen in healthy kidney donors. However, an abnormal circadian BP rhythm is associated with acceleration of the progression of nephropathy [22], and nocturnal nondipping is also associated with left ventricular hypertrophy, carotid wall thickening, cerebral infarcts, and cognitive impairment [16]. The prospective demonstration of absence of an unfavourable prognosis with nocturnal nondipping in this study provides further reassurance to donors. Nevertheless, long-term prospective studies are required to confirm these findings and determine whether an abnormal BP or circadian rhythm has similar implications for kidney donors who do develop these conditions. Prospective studies, however, are rare. In a study of 148 predominantly white donors, 24 of who were classified as hypertensive prior to donation, ABP was not higher at 6 to 12 months postdonation [23]. The 24-h SBP in this study decreased in dippers and remained unchanged in nondippers. While we speculate that this may have been caused by repeated measurements and resultant greater donor comfort with 24-h ABP monitoring, the observation that the BP did not increase is very reassuring. Our study therefore provides additional information on ABP-related changes and their impact post kidney donation.

While level of renal function as estimated by the SCr and 24-h urine CCr demonstrated an expected decrease after nephrectomy, the study is limited by the lack of a gold standard for measurement of renal function, such as iothalamate or inulin clearance. These methods were not utilized in order to avoid a precipitous reduction in the recruitment rate for the study, to which only 53% could be recruited despite its observational nature, leading to immeasurable selection bias (e.g. from health-related habits). A bigger pool of donors recruited through a multi-centre study will provide more representative results, and also allow for stratification by demographics. Extended study of these subjects to 5 years and beyond, comparing them to matched controls will also yield useful insights. It is important to point out that some donors had a postdonation CCr as low as 36 ml/min/1.73 m<sup>2</sup>, placing them in a renal function range comparable to Stage III chronic kidney disease (Table 2, Fig. 1). It would therefore seem

highly desirable to ensure that postdonation monitoring at a minimum be made available to all donors and thereby allow for identifying subsets of donors who require more intense follow-up. All such donors identified in this study were referred to their predonation nephrologists. Our study is also limited to measurement of the 24-h protein excretion rate rather than microalbuminuria, which may have yielded additional information.

There is some concern that loss of renal mass can lead to glucose intolerance. In a study of 28 rats subjected to unilateral nephrectomy, glucose intolerance was noted [24]. Other groups have demonstrated increases in body weight and triglycerides [25] and development of the metabolic syndrome [15]. This study provides some reassurance that traditional markers of cardiovascular risk are not increased in living donors, at least in the short term. A trend towards increase in triglyceride (TG) levels was noted but firm conclusions cannot be made because of absence of statistical significance of the finding and multiple comparisons made in this analysis, which could produce such results by chance alone. Additional follow-up is warranted.

In summary, living kidney donation, while resulting in a significant decline of renal function, could not be associated in this study with an increase in BP, protein excretion, or other metabolic risk factors over one year. Predonation nocturnal nondipping does not seem to carry adverse consequences over 12 months.

## Authorship

GVRP: Study concept, design, and funding; data analysis; manuscript preparation and revision. DL: Data collection and entry. SS: Patient recruitment and data entry. MH: Statistical data analysis. MMN: Patient recruitment, data collection and data entry. LR: Patient recruitment, data collection, data entry, manuscript preparation.

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