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Original Article

Nephrectomy for kidney tumour increases the risk of *de novo* arterial hypertension

Pierre Bigot[1], Jean-Christophe Bernhard[2], Zine-Eddine Khene[3], Charles Dariane[4], Souhil Lebdai[1], Nicolas Doumerc[5], François Xavier Nouhaud[6], Idir Ouzaid[7], Patrick Saulnier[8], Arnaud Méjean[4], Morgan Roupret[9], Karim Bensalah[3] and and the French Committee of Urologic Oncology

[1]Department of Urology, Angers University Hospital, Angers, [2]Department of Urology, Bordeaux University Hospital, Bordeaux, [3]Department of Urology, Rennes University Hospital, Rennes, [4]Department of Urology, Hôpital Européen Georges-Pompidou, Paris, [5]Department of Urology, CHU de Toulouse, Toulouse, [6]Department of Urology, Rouen University Hospital, Rouen, [7]Department of Urology, Angers University Hospital, Paris, [8]Department of Biostatistics, Angers University Hospital, Angers, and [9]Department of Urology, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France

Objective

To evaluate prospectively the effects of surgical excision of renal tumours on blood pressure (BP).

Patients and Methods

In a multicentre prospective study, we evaluated 200 patients who underwent nephrectomy for renal tumour between 2018 and 2020 at seven departments of the French Network for Kidney Cancer, the UroCCR. All patients had localized cancer without pre-existing hypertension (HTN). Blood pressure was measured the week before nephrectomy, and at 1 month and 6 months after nephrectomy, according to the recommendations for home BP monitoring. Plasma renin was measured 1 week before surgery and 6 months after surgery. The primary endpoint was the occurrence of *de novo* HTN. The secondary endpoint was clinically significant increase in BP at 6 months, defined by an increase in systolic and/or diastolic ambulatory BP ≥10 mmHg or requirement for medical antihypertensive treatment.

Results

Blood pressure and renin measurements were available for 182 (91%) and 136 patients (68%), respectively. We excluded from the analysis 18 patients who had undeclared HTN detected on preoperative measurements. At 6 months, 31 patients (19.2%) had *de novo* HTN and 43 patients (26.3%) had a significant increase in their BP. Type of surgery was not associated with an increased risk of HTN (21.7% partial nephrectomy [PN] vs 15.7% radical nephrectomy [RN]; $P = 0.59$). There was no difference between plasmatic renin levels before and after surgery (18.5 vs 16; $P = 0.46$). In multivariable analysis, age (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.02–1.12; $P = 0.03$) and body mass index (OR 1.14, 95% CI 1.03–1.26; $P = 0.01$) were the only predictors of *de novo* HTN.

Conclusion

Surgical treatment of renal tumours is associated with significant changes in BP, with *de novo* HTN occurring in almost 20% of the patients. These changes are not impacted by the type of surgery (PN vs RN). Patients who are scheduled to undergo kidney cancer surgery should be informed of these findings and have their BP closely monitored after the operation.

Keywords

renal cancer, radical nephrectomy, partial nephrectomy, blood pressure, hypertension, renin, surgery

Introduction

Renal cell carcinoma represents 3% of all cancers. When the tumour is localized to the kidney, patients are optimally treated by partial (PN) or radical nephrectomy (RN) [1]. It is well known that PN better preserves renal function and could prevent chronic kidney disease [2]. The impact of kidney surgery on arterial blood pressure (BP) regulation, however, is not well known. Living kidney donors have a long-term increased risk of cardiovascular complications with an increased prevalence of arterial hypertension (HTN) [3]. This HTN risk after nephrectomy was confirmed in animal models [4]. Renal afferent and efferent sympathetic nerves are involved in BP regulation. The contribution of renal sympathetic overactivity to the development of HTN is well established [5]. Renal nerves can stimulate renin secretion, and it is likely that the suppression of sympathetic activity impairs the ability of the renin-angiotensin system to regulate renal perfusion and arterial blood flow [6].

During kidney surgery, the renal artery is often dissected and clamped. PN also requires parenchymal sutures, which can lead to stenosis of distal arterial branches and increase renin secretion and BP. This mechanism is responsible for renovascular HTN in case of renal artery stenosis [7]. Secondary HTN is also commonly observed after kidney trauma [8].

The impact of kidney surgery on BP is unclear and there is very little information in the literature. The aim of this study, therefore, was to prospectively evaluate the consequences of surgical excision of renal tumours on BP.

Patients and Methods

The VAPANCR trial (NCT 03218319) was designed in collaboration with the Cancerology Committee of the French Association of Urology and was sponsored by the French Association of Urology. The conduct of the trial conformed to the International Conference on Harmonization E6 guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The study obtained approval from Ethical Committee (2017-A00127-46) and was carried out according to the framework of the UroCCR (the French Network for Kidney Cancer) project (NCT03293563).

We prospectively included 200 patients who underwent nephrectomy for a renal tumour between January 2018 and September 2020 at seven university hospitals from the UroCCR network. Inclusion criteria were a single localized kidney tumour eligible for nephrectomy and the absence of pre-existing HTN.

All BP measurements were acquired using a validated ambulatory automated oscillometric device (Fahrenheit medical TMB-1491). BP evaluations were performed according to standard guidelines for ambulatory home BP measurements 1 week before surgery, 1 month after surgery and 6 months after surgery [9]. After 5 min of seated rest and before any medication was taken, the patients performed four measurements in the morning before breakfast and four in the evening before bedtime. The first morning and evening measurements were discarded and the remaining three readings (i.e., 18 readings) were averaged for 3 days. The threshold for HTN was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.4 (i.e., systolic BP >140 mmHg and/or diastolic BP >90 Hg).

Glomerular filtration rate derived from the Modification of Diet in Renal Disease Study Group equation was assessed before surgery, and at 1 month and 6 months after surgery. Plasma renin was measured 1 week before surgery and 6 months after surgery in patients who neither took any drugs likely to interact with the renin-angiotensin-aldosterone system nor were on a salt-free diet. Blood samples were obtained in the morning following a 12-h fasting period and after 45 min of rest in a lying position.

We prospectively collected preoperative clinical data (age, gender, body mass index [BMI], GFR), operative data (surgery type [RN vs PN], operative renal artery clamping) and histological subtype, stage T and tumour size at final specimen analysis.

Our primary endpoint was the occurrence of HTN at 6 months, defined as (1) systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or (2) *de novo* use of antihypertensive medications.

Our secondary endpoint was the occurrence of a clinically significant increase in BP at 6 months. An increase in BP was considered clinically significant if the variation in systolic and/or diastolic ambulatory BP was ≥10 mmHg or if medical antihypertensive treatment was required.

A third endpoint was the occurrence of a significant decrease in BP, defined as a decrease in systolic/or diastolic ambulatory BP ≤10 mmHg.

Finally, we compared the evolution of renin secretion at 1 month and 6 months after surgery.

The variations in BP before and after surgery were compared using a Wilcoxon test. We also analysed the factors that were associated with the occurrence of a significant change in BP. Qualitative data were compared using chi-squared or Fisher's exact tests and quantitative data using a Mann–Whitney test. Multivariate analysis was performed using a logistic regression model on patients who developed new and/or clinically significant change in BP at 6 months.

Results

Patient Characteristics

We included 200 patients but only 182 (91%) had evaluable BP measurements and were considered for the final analysis. We excluded from the analysis 18 patients who had undeclared HTN detected on preoperative measurements (Figure S1). Among included patients, 136 (74.7%) had an exploitable renin measurement. Baseline characteristics are presented in Table 1. Overall, 34 (20.9%) and 129 patients (79.1%) were treated with RN and PN, respectively.

Blood Pressure Changes

De novo HTN was observed at 1 month and 6 months in 23 (14.3%) and 31 patients (19.2%). Seven patients (4.3%)

Table 1 Patient characteristics, surgery type and disease characteristics (*n* = 163).

Median (range) age, years	54 (21–85)
Sex: male, *n* (%)	88 (75)
Median (range) BMI	25 (18.7–41)
Median (range) tumour size, cm	4.3 (1–13)
Median (range) GFR, mL/min	93.8 (15.7–168)
Preoperative chronic kidney disease, *n* (%)	6 (3.7)
Type of surgery, *n* (%)	
Radical nephrectomy	34 (20.9)
Partial nephrectomy	129 (79.1)
Off-clamp	57 (44.2)
Arterial clamping	72 (55.8)
Histological type, *n* (%)	
Benign	23 (14.1)
Malignant	140 (85.9)
Tumour stage for malignant tumours, *n* (%)	140
T1	98 (70)
T2	11 (7.9)
T3	31 (22.1)

BMI, body mass index.

required antihypertensive treatment. Significant increases in BP were seen in 17 (10.3%) and 43 patients (26.3%), at 1 and 6 months, respectively (Fig. 1). Significant decreases in BP were seen in 15 patients (9%) at 6 months after surgery. Figure 2 shows the changes in systolic and diastolic BP before surgery, 1 month after surgery and 6 months after surgery. Patients (*n* = 7) who initiated antihypertensive treatment during the study were excluded from the figure.

Renin Secretion Changes

The average renin level preoperatively and postoperatively was 18.5 and 16 IU, respectively (*P* = 0.45). Mean baseline variations at 6 months in patients treated with RN and PN were −8 and +3 UI/L, respectively (*P* = 0.005).

Risk Factors for *de novo* Hypertension at 6 months

In univariate and multivariate analysis, age (odds ratio [OR] 1.07, 95% CI 1.02–1.12; *P* = 0.03) and BMI (OR 1.14, 95% CI 1.03–1.26; *P* = 0.01) were associated with an increased risk of postoperative HTN (Table 2).

Risk Factors for a Clinically Significant Increase in Blood Pressure at 6 months

In univariate and multivariate analysis, male gender (OR 2.7, 95% CI 1.1–7.1; *P* = 0.029) and age (OR 1.05, 95% CI 1.01–1.09; *P* = 0.016) were associated with an increased risk of significant postoperative augmentation of BP (Table S1).

Influence of Type of Surgery on Postoperative Blood Pressure and Renin Secretion

Type of surgery (RN vs PN) was not associated with the risk of HTN or changes in BP. In case of PN, arterial clamping was not associated with an increased risk of HTN. Renin secretion was decreased after RN and increased after PN. In the PN subgroup, renin secretion was not influenced by the type of technique used (off-clamp or arterial clamping; Table 3).

Discussion

Hypertension is a major disease burden, leading to 9.4 million deaths and the loss of 212 million healthy life-years (8.5% of the global total) each year [10]. Prospective

Fig. 1 Changes in arterial blood pressure (BP) after renal surgery (*n* = 163). *A change in BP was considered clinically significant if the variation in systolic and/or diastolic ambulatory BP was ≥10 mmHg or if medical antihypertensive treatment was required.

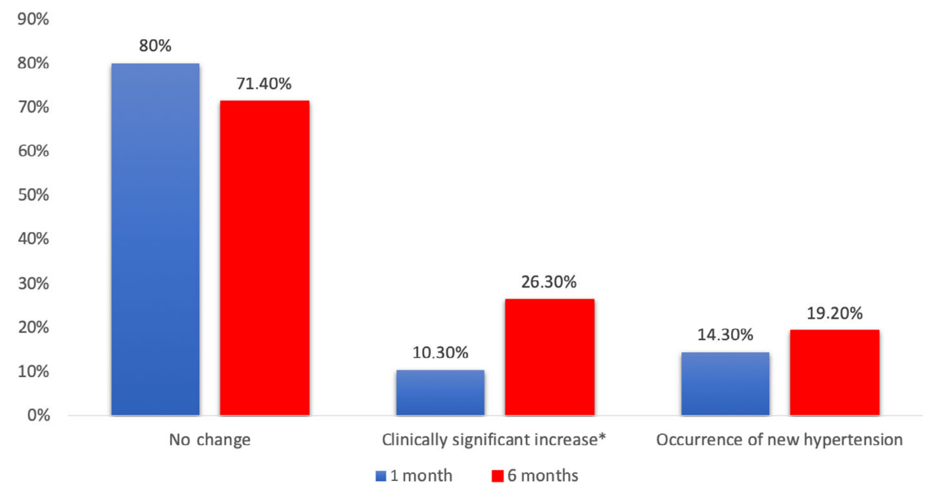

Fig. 2 Mean blood pressure of the patient cohort before, 1 month after surgery and 6 months after surgery (*n* = 156). Patients who initiated antihypertensive treatment were excluded from the analysis (*n* = 7). DBP, diastolic blood pressure; SBP, systolic blood pressure.

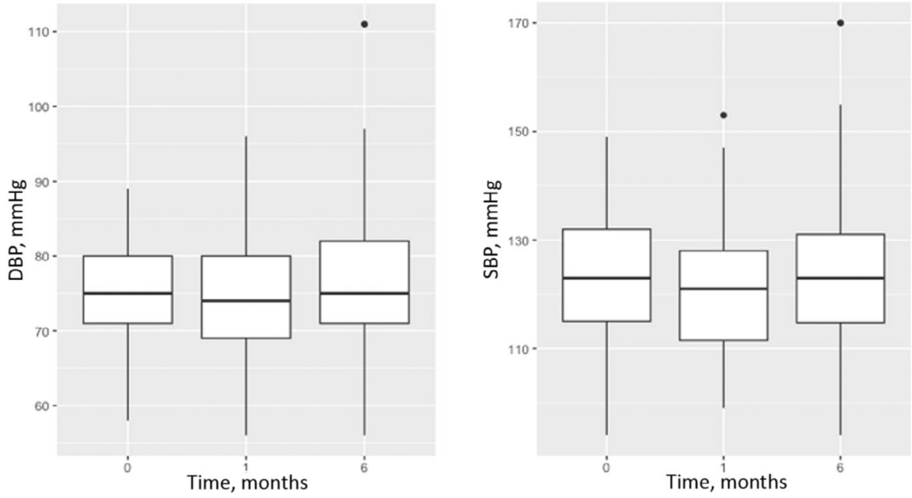

Table 2 Univariate and multivariate analysis of predictive factors for new arterial hypertension 6 months after nephrectomy for renal tumour.

Factor	Univariate			Multivariate		
	P	OR	CI	*P*	OR	CI
Age (per increasing age)	0.004	1.07	1.02–1.12	0.03	1.07	1.02–1.12
BMI (per unit of BMI increase)	0.014	1.12	1.02–1.23	0.011	1.14	1.03–1.26
Sex (male vs female)	0.36	0.66	0.26–1.59			
Preoperative kidney function (normal vs chronic kidney disease)	0.24	2.82	0.37–15.3			
Tumour size (continuous)	0.95	1	0.84–3.3			
Tumour stage (T1 vs others)	0.84	1.11	0.41–3.33			
Type of surgery (RN vs PN)	0.59	1.32	0.45–3.49			
Histological types (benign vs malignant tumours)	0.38	1.96	0.52–12.7			
Peri-operative complications	0.73	1.47	0.07–10.4			
Operative time	0.91	1	0.99–1.01			

OR, odds ratio; PN, partial nephrectomy; RN, radical nephrectomy.

Table 3 Influence of type of surgery on blood pressure and renin secretion outcomes.

	New HTN, *n* (%)	*P*	Significant ambulatory BP changes	*P*	Mean renin variation, IU	*P*
Nephrectomy type		0.59		0.52		0.005
RN (*n* = 34)	6 (15)		7 (20.6)		−8.08	
PN (*n* = 129)	28 (21.7)		22 (17.05)		3.12	
PN type		0.95		0.70		0.77
Off-clamp (*n* = 56)	8 (14.3)		10 (17.86)		4.14	
Arterial clamping (*n* = 72)	10 (13.89)		11 (15.28%)		2.58	

Abbreviations: BP, blood pressure; HTN, hypertension; PN, partial nephrectomy; RN, radical nephrectomy.

observational studies have repeatedly demonstrated a strong, continuous positive relationship between HTN and cardiovascular death, with no evidence of a threshold [11–13]. In individuals aged 40–69 years, a 20-mmHg rise in systolic BP or a 10-mmHg rise in diastolic BP regardless of baseline values is associated with an increased risk for stroke or ischaemic heart disease. A systolic BP reduction of 5 mmHg can decrease stroke mortality by 14% and cardiovascular mortality by 9% [11]. In addition, cardiovascular events in individuals with HTN tend to occur 5 years earlier than in individuals with lower levels of BP [12]. Moreover, strong positive associations were found between premature stroke mortality and mean systolic BP [14].

The scientific literature concerning variations in BP after renal surgery is sparse, contradictory and limited by a poor level of evidence (only retrospective cohort descriptions), absence of precise monitoring of BP, and lack of data concerning the use of antihypertensive therapy [15–19]. In the largest retrospective study (292 patients), Gupta et al. [19] noted minor changes in BP but a significant increase in the use of antihypertensive drugs after surgery. Other authors reported an increased risk of HTN after PN compared to RN [16,17].

In our prospective evaluation, we found an incidence of almost 20% of *de novo* HTN 6 months after renal surgery. The follow-up was too short to evaluate a further impact on the occurrence of cardiovascular events; however, 6 months after surgery, we did not observe any major cardiovascular event (stroke or myocardial infarction).

Partial nephrectomy has been shown to better preserve renal function and could potentially reduce the risk of cardiovascular mortality and one can hypothesize that the type of surgery could influence the regulation of BP. In our study, there was no evidence of an increased risk of HTN depending on the type of surgery (RN or PN) or the technique used during the PN (arterial clamping or no clamping).

The renin-angiotensin system plays an important role in the regulation of BP and the onset of secondary HTN. Therefore, we monitored changes in renin secretion 6 months after surgery. The measurement of renin activity is cumbersome and must be done after 1 h of rest. For this reason, we were only able to obtain 136 interpretable samples. We did not find any evidence that changes in BP could be related to variations in renin secretion. Surprisingly, we found a decrease in renin levels after RN but an increase after PN. The impact of renin secretion on BP needs to be explored in a larger cohort of patients with a longer follow-up.

We designed our study taking great care to measure BP according to current recommendations. Although ambulatory BP monitoring is the 'gold standard' BP measurement, home BP monitoring is recommended as a more practical and less expensive alternative [20]. Recognition and use of home BP monitoring have increased and current HTN guidelines make strong recommendations for the use of out-of-office BP monitoring techniques, including home BP monitoring and ambulatory BP monitoring [21]. The value of home BP monitoring is highlighted by data from multiple studies showing that HTN is an important predictor of target organ damage, and cardiovascular disease and stroke-related morbidity and mortality, and provides better prognostic information than office BP [22,23]. Guo et al. [24] reported that the coefficients of variation between two home BP measurements (median interval between the two repeated recordings of 13 days) were 5.1% and 4.5% for home morning systolic and diastolic BP, respectively. This confirms the reproducibility of home BP monitoring. It has also been shown that variability in systolic BP and diastolic BP across visits of 5.4 and 5 mmHg was significantly associated with an increased risk of all cardiovascular mortality outcomes [25].

In our study, 26% of our patients showed a significant increase in BP. We believe this shows that careful monitoring of BP after kidney cancer surgery should be targeted to potentially prevent cardiovascular events.

Although carefully designed, our study is limited by the absence of a comparator control group. However, the rapid and persistent changes in BP in some patients was unexpected. We cannot conclude that this HTN is directly linked to the surgery, but we can advise monitoring the BP of patients after kidney surgery because the occurrence of HTN was a frequent event after surgery. Furthermore, we can agree that such a large number of patients with new HTN 6 months after surgery is not physiological in a population whose average age is 54 years. Also, our population is not representative of the usual patients undergoing surgery for a renal tumour, many of whom have HTN [26]. This is explained by the fact that we had to exclude patients with HTN or those receiving antihypertensive treatment in order to interpret BP variations objectively.

In conclusion, surgical treatment of renal tumours was associated with significant changes in BP with *de novo* HTN occurring in almost 20% of the patients. These changes were not impacted by the type of surgery (PN vs RN). Longer follow-up is necessary to determine whether this rise in BP will increase the occurrence of cardiovascular events. These important changes in BP after renal surgery justify preoperative information and postoperative monitoring of BP.

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Disclosure of Interests

All authors state they have no conflict of interest that are directly or indirectly related to the research.

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Correspondence: Pierre Bigot, Department of Urology, Angers University Hospital, 4, rue Larrey – 49 933 Angers Cedex 9, France.

e-mail: pibigot@chu-angers.fr

Abbreviations: BMI, body mass index; HTN, hypertension; OR, odds ratio; PN, partial nephrectomy; RN, radical nephrectomy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart.

Table S1. Univariate and multivariate analysis of predictive factors for clinically significant changes in BP at 6 months after nephrectomy for renal tumour.

