Temporary Renal Ischemia During Nephron Sparing Surgery is Associated With Short-Term but Not Long-Term Impairment in Renal Function

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Purpose: The emergence of laparoscopic nephron sparing surgery has rekindled interest in the impact of warm renal ischemia on renal function. To provide data with which warm renal ischemia can be compared we analyzed short-term and long-term changes in the glomerular filtration rate after temporary cold renal ischemia.

Materials and Methods: In patients undergoing open nephron sparing surgery the estimated glomerular filtration rate was assessed preoperatively, early in the postoperative hospital stay, and 1 and 12 months after surgery using the abbreviated Modification of Diet in Renal Disease Study equation. We separately analyzed 70 patients with a solitary kidney and 592 with 2 functioning kidneys. The end point was the percent change from the baseline glomerular filtration rate. A linear regression model was used to test the association between the glomerular filtration rate change, and ischemia time, patient age, tumor size, estimated blood loss and intraoperative fluid administration.

Results: Median cold ischemia time was 31 minutes in patients with a solitary kidney and 35 minutes in those with 2 kidneys. Compared to patients with 2 kidneys those with a solitary kidney had a significantly lower preoperative estimated glomerular filtration rate ($p < 0.001$), which decreased a median of 30% during the early postoperative period, and 15% and 32% 1 and 12 months after surgery, respectively. In patients with 2 kidneys the corresponding glomerular filtration rate decreases were 16%, 13% and 14%, respectively. On multivariate analyses in each group cold ischemia duration and intraoperative blood loss were significantly associated with early glomerular filtration rate changes. However, 12 months after surgery age was the only independent predictor of a glomerular filtration rate decrease in patients with 2 kidneys.

Conclusions: Cold renal ischemia during nephron sparing surgery is a significant determinant of the short-term postoperative glomerular filtration rate. Longer clamping time is particularly detrimental in patients with a solitary kidney but it does not appear to influence long-term renal function. Patients of advanced age may be less likely to recover from acute ischemic renal injury.

Key Words: kidney; kidney neoplasms; carcinoma, renal cell; ischemia

Nephron sparing surgery is currently considered the gold standard curative operation in patients who present with a single, small (less than 4 cm), localized renal cell carcinoma.[1] NSS provides excellent cancer control and compared to removal of the entire kidney nephron preservation is believed to decrease the risk of progression to chronic renal insufficiency.[2]

Paralleling the application of minimally invasive techniques in other areas of urology, laparoscopic NSS has gained popularity in recent years. Several experienced groups have now reported equivalent short-term oncological outcomes and improved convalescence compared to those of the open approach.[3–6] With growing experience the indications for laparoscopic NSS have expanded to include larger tumors and those at more challenging locations.[5,7] To facilitate safe tumor resection and minimize intraoperative blood loss investigators have generally performed temporary occlusion of the vascular pedicle.[4,8] However, because laparoscopic techniques for acquiring renal hypothermia and protecting the kidney from ischemic damage have yet to be fully developed, interest has been rekindled in the impact of warm renal ischemia on renal function.[7,9–12] This concern is further accentuated when NSS is performed in the setting of a solitary kidney or for large, centrally located renal masses requiring prolonged vascular occlusion.[5,7]

The impact of warm renal ischemia on renal function is not yet fully understood. Some studies indicate that the clinical sequela is minimal when warm renal ischemia lasts approximately 30 minutes or even up to 55 minutes.[9,10] Others concluded that laparoscopic clamping of the renal artery in a normothermic environment should be done even for small and superficial tumors.[11] However, these analyses were generally limited by small sample size or the use of serum creatinine as a measure of renal function. Because GFR must decrease to approximately half the normal level before serum creatinine attains its upper normal limit, serum creatinine should not be used as the only means of evaluating kidney function. According to practice guidelines set forth by the National Kidney Foundation accurate as-

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sessment of renal function should be based on an estimation of GFR from equations that consider serum creatinine as well as patient age, sex, race and body size.[13]

The impact of cold ischemia on renal function in the context of NSS is also not well documented. The basis of our current practice patterns in renal cancer comes from several animal and human studies from the 1970s, which established kidney tolerance to normothermic and hypothermic ischemic insult.[14,15] However, these studies were not done during the modern era of NSS and, therefore, it is inappropriate to extrapolate those findings to a clinical setting, where hemodynamic changes and parenchymal loss occur.

Warm and cold renal ischemia continues to be widely used in open as well as in laparoscopic NSS. In a large contemporary series of open NSS pedicle clamping was avoided in 50% of cases, warm ischemia was used for a short duration of a median of 12 minutes in 32% and cold ischemia was used for a median of 27 minutes in 18%.[16] To better understand the impact of cold renal ischemia and provide data with which warm ischemia can be compared we analyzed the short-term and long-term effect of transient cold renal ischemia on renal function in a large cohort of patients undergoing NSS.

MATERIALS AND METHODS

After institutional review board approval was received our prospectively updated renal cancer database was reviewed to identify 662 patients undergoing NSS for a renal tumor between 1989 and 2004. During the study years our general practice was to perform tumor resection following occlusion of the renal vascular pedicle. Clamping was avoided at the discretion of the attending surgeon in cases of small and exophytic lesions. Adjunct renoprotective measures were routinely used, including vigorous intravenous hydration, avoidance of intraoperative hypotension and intravenous administration of 12.5 gm mannitol in 200 ml saline, preceding occlusion of the vessels, followed by surface parenchymal hypothermia using sterile ice slush. Ischemia time was retrieved from the operation notes and defined as the duration between occlusion and unclamping of the renal vascular pedicle.

In all patients serum creatinine values (SCr) were available before and after the operation. Renal function was assessed by estimating GFR using the abbreviated Modification of Diet in Renal Disease study equation, GFR in ml per minute per 1.73 $m^2 = 186 \times SCr^{-1.154} \times age^{-0.203} \times$ (0.742 if female) $\times$ (1.210 if black).[17] The end point was the percent change in GFR, defined as the difference between postoperative and baseline GFR divided by baseline GFR. The outcome was analyzed at 3 intervals following surgery, namely the early postoperative period (the peak change in GFR recorded during hospital stay), and the 1-month and 1-year followup visits.

We hypothesized that several factors may affect postoperative GFR, and so a linear regression model was fitted to test whether ischemia time had an independent impact on renal function after adjusting for patient age at surgery, tumor size (defined as maximal tumor diameter), the amount of intraoperative fluid administration and estimated blood loss. To avoid potential bias ischemia time was included in the model as a continuous variable rather than categorized into predefined intervals and incorporated as zero in cases in which the vascular pedicle was not occluded. We excluded the intercept (constant term) from the linear regression model because we expected the percent change in GFR to be zero when ischemia time and all other covariates were zero. Because any change in operated kidney function may become completely obscured by the opposite kidney, we separately analyzed 592 patients with 2 functioning kidneys at surgery and the 70 with a solitary kidney. Of the former patients 95 did not have clamping time available and they were excluded from the multivariate model. The t test was used to test differences in serum creatinine and estimated GFR between the groups. All analyses were performed using SPSS®, version 10.0 with $p < 0.05$ considered significant.

RESULTS

Table 1 lists clinical characteristics and ischemia time in all patients. The median ischemia duration was 35 minutes (range 14 to 103) in patients with 2 functioning kidneys and 31 minutes (range 15 to 90) in patients with a solitary kidney. While vascular clamping was avoided in 11% of the patients with 2 kidneys and in 27% of those with a solitary kidney, an ischemia time of 30 minutes or longer was recorded in 56% and 50%, respectively (table 1). Preoperative serum creatinine did not differ significantly between patients with 2 kidneys or a solitary kidney (table 1, p = 0.22). However, patients with a solitary kidney had a significantly lower preoperative estimated GFR, reflecting the inability of serum creatinine to accurately determine renal function (see figure and table 1, $p < 0.001$). The figure and table 1 also show changes in GFR during the early postoperative period, and at the 1-month and 1-year followups. Temporary hemodialysis was required in 4 of the 70 patients (5.7%) undergoing NSS for tumor in a solitary kidney, of whom all were free of dialysis at the 1-month followup. Ischemia time in

TABLE 1. *Characteristics, clamping time and GFR changes in patients undergoing NSS*

	2 Functioning Kidneys	Solitary Kidney
No. pts	592	70
Mean age (IQR)	61 (51, 70)	62 (58, 71)
No. sex (%):		
M	343 (58)	52 (74)
F	249 (42)	18 (26)
No. ischemia time (%):		
No clamping	66 (11)	19 (27)
20 Mins or less	14 (2)	5 (7)
21–30 Mins	83 (14)	11 (16)
31–40 Mins	127 (22)	13 (19)
41–50 Mins	125 (21)	13 (19)
51–60 Mins	57 (10)	1 (1)
Greater than 61 mins	25 (4)	8 (11)
Not available*	95 (16)	—
Median ml estimated blood loss (IQR)	300 (200, 500)	550 (330, 975)
Median l intraop fluids (IQR)	3.5 (3, 4.5)	4.2 (3.5, 5.1)
Median cm tumor size (IQR)	2.5 (1.8, 3.5)	3.5 (2.5, 4.5)
Median mg/dl preop serum creatinine (IQR)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)
Median preop ml/min/1.73 m^2 estimated GFR (IQR)	70.2 (59.6, 81.8)	52.9 (46, 62.9)
Median % GFR change (IQR):		
Early postop	−16 (−32, 0)	−30 (−12, −53)
1-Mo followup	−13 (−25, 0)	−15 (−33, 0)
1-Yr followup	−14 (−30, 0)	−32 (−46, −6)

* Cold renal ischemia was documented but accurate clamping time was unavailable.