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Selective Versus Nonselective Arterial Clamping During Laparoscopic Partial Nephrectomy: Impact upon Renal Function in the Setting of a Solitary Kidney in a Porcine Model

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Abstract

Introduction: Laparoscopic partial nephrectomy has emerged as a standard of care for small renal masses. Nevertheless, there remains concern over the potential for irreversible insult to the kidney as a result of exposure to warm ischemia. We aim to investigate the utility of selective segmental arterial clamping as a means to reduce the potential for ischemic damage to a solitary kidney during laparoscopic partial nephrectomy utilizing a porcine model.
Materials and Methods: A total of 20 domestic swine were randomized into four equal groups. Each subject underwent laparoscopic radical nephrectomy to create the condition of a solitary kidney. On the contralateral side, a laparoscopic lower pole partial nephrectomy was performed, employing either selective or nonselective vascular clamping for either 60 or 90 minutes. Postoperatively, clinical status and serial serum studies were closely monitored for 1 week.
Results: There were no intraoperative complications. The 90-minute nonselective clamping produced devastating effects, resulting in rapid deterioration into florid renal failure within 72 hours. The 60-minute nonselective clamping group experienced modest but significant rises in both blood urea nitrogen and creatinine. Both 60- and 90-minute selective clamping groups performed well, with no significant rises in creatinine over a 7-day period, and no instances of renal failure.
Conclusions: Selective arterial clamping is a safe and feasible means of vascular control during laparoscopic partial nephrectomy. In the porcine model, selective clamping appears to improve functional outcomes during prolonged periods of warm ischemic insult. Prospective evaluation of the technique in humans is necessary to determine if selective arterial control confers long-term functional benefits in patients with limited renal reserve.

Introduction

Since its introduction in 1993, laparoscopic partial nephrectomy has emerged as a standard of care for the management of small renal masses.[1–4] During critical portions of the procedure, arterial clamping is routinely necessary to provide a relatively bloodless field for tumor dissection and to minimize intraoperative blood loss. However, the potential for ischemic damage to the remaining renal parenchyma remains a concern.

While some studies have found that the impact of short-term warm ischemia upon postoperative renal function is negligible,[5,6] and compares favorably to total loss of the renal unit by radical nephrectomy,[7] it is possible that the renal reserve provided by a normal contralateral kidney may mask the loss of renal function to a considerable degree. Indeed, studies evaluating functional outcomes of partial nephrectomy in the setting of a solitary kidney favor the open approach, as cold ischemia and shorter overall ischemic times appear to provide superior preservation of functional renal reserve.[8,9]

As a result, recent interest has focused upon techniques to minimize the potential for warm ischemic injury during minimally invasive nephron-sparing surgery. Techniques such as selective arterial embolization,[10] "on-demand" clamping,[11] and early clamp release[12] have been described, all of which have demonstrated promising early results.

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Table 1. Changes in Blood Urea Nitrogen over the Period of Observation

Subject	*Clamp type*	*Clamp time (min)*	*Baseline*	*1 Day*	*2 Days*	*7 Days*
1	Selective	60	6	10	10	11
2	Selective	60	10	13	12	16
3	Selective	60	6	10	10	13
4	Selective	60	12	15	13	13
5	Selective	60	10	18	18	20
6	Selective	90	12	15	15	15
7	Selective	90	11	16	16	15
8	Selective	90	6	10	10	13
9	Selective	90	8	16	18	22
10	Selective	90	11	20	14	18
11	Nonselective	60	8	18	22	45
12	Nonselective	60	12	20	28	20
13	Nonselective	60	10	22	20	28
14	Nonselective	60	9	19	22	25
15	Nonselective	60	10	22	20	44
16	Nonselective	90	15	56	105	N/A
17	Nonselective	90	9	45	N/A	N/A
18	Nonselective	90	10	63	88	N/A
19	Nonselective	90	6	69	96	N/A
20	Nonselective	90	13	73	80	N/A

N/A = not applicable.

As the segmental renal arteries are end-arteries and, therefore, do not communicate, we sought to investigate the utility of selective segmental arterial clamping as a means to reduce the potential for ischemic damage to the kidney during partial nephrectomy utilizing a porcine model.

Materials and Methods

After approval by our Institutional Animal Care and Use Committee, a total of 20 female domestic pigs (Oak Hill Genetics, Ewing, IL) were prospectively randomized into four equal investigational groups to undergo nonselective and selective segmental arterial clamping for periods of 60 and 90 minutes. Normal preoperative renal function was determined by baseline laboratory studies, as detailed in Tables 1 and 2.

All animals were placed under general endotracheal anesthesia for operative intervention after being premedicated with intramuscular buprenorphine at 0.05 mg/kg. A 16F Foley catheter was placed under anesthesia to monitor intraoperative and postoperative urine output.

After placing the animal in a lateral decubitus position, a Veress needle was utilized to achieve pneumoperitoneum with carbon dioxide; pressure was consistently maintained at 12 to 15 mm Hg. A laparoscopic nephrectomy was then per-

Table 2. Changes in Creatinine over the Period of Observation

Subject	*Clamp type*	*Clamp time (min)*	*Baseline*	*1 Day*	*2 Days*	*7 Days*
1	Selective	60	0.7	0.9	0.9	1.0
2	Selective	60	0.9	0.9	0.9	1.4
3	Selective	60	0.8	1.2	1.0	1.0
4	Selective	60	1.2	1.4	1.0	1.1
5	Selective	60	0.8	1.2	1.1	1.2
6	Selective	90	0.8	0.9	0.9	1.8
7	Selective	90	1.3	0.9	0.9	1.0
8	Selective	90	1.4	1.6	1.6	1.8
9	Selective	90	0.7	1.4	1.4	1.4
10	Selective	90	1.6	1.7	1.7	1.7
11	Nonselective	60	1.5	1.8	1.8	2.0
12	Nonselective	60	1.3	1.4	1.4	2.1
13	Nonselective	60	0.7	2.0	2.0	2.0
14	Nonselective	60	1.4	1.8	2.0	2.0
15	Nonselective	60	0.8	1.6	2.0	1.0
16	Nonselective	90	1.3	8.0	13.0	N/A
17	Nonselective	90	1.6	9.4	N/A	N/A
18	Nonselective	90	0.8	6.0	7.7	N/A
19	Nonselective	90	1.0	7.3	9.1	N/A
20	Nonselective	90	1.4	6.4	7.6	N/A

N/A = not applicable.

formed utilizing standard technique to create the condition of a solitary kidney in each subject. The kidney was left *in situ* for later retrieval with the partial nephrectomy specimen. The trocars were then removed, and all incisions were closed.

For the contralateral partial nephrectomy, the subjects were then placed in the opposite lateral decubitus position and pneumoperitoneum was once again established. Utilizing standard laparoscopic techniques, the renal hilum was carefully dissected, taking great care not to injure critical structures. The renal artery and its branches were meticulously dissected and exposed in full, and the lower pole segmental artery was clearly identified in all cases.

Groups 1 and 2 ($n = 5$ each) underwent nonselective clamping for 60 and 90 minutes, respectively. To accomplish this, the main renal artery was clamped using laparoscopic bulldog clamps, and the kidney was monitored to ensure pallor of the entire kidney.

Groups 3 and 4 ($n = 5$ each) underwent selective clamping of the segmental artery supplying the lower pole using a bulldog clamp, for a period of 60 and 90 minutes, respectively (Fig. 1). The lower pole of the kidney was examined for pallor to confirm complete vascular occlusion; the remainder of the kidney remained perfused in this cohort (Fig. 2).

For all subjects, a laparoscopic lower pole partial nephrectomy was then performed using cold shears for dissection. Every attempt was made to excise equivalent amounts of renal parenchyma in each subject. Renorrhaphy was then performed using 2-0 polyglactin sutures and Lapra-Ty (Ethicon, Cincinnati, OH) clips.

After 60 or 90 minutes, depending upon randomization, the arterial clamp was released. The radical and partial nephrectomy specimens were then extracted, the incisions were closed, and the animals were recovered. Postoperative analgesia was provided with buprenorphine and carprofen as needed.

Serum chemistries were evaluated at baseline, and at 1, 2, and 7 days postoperatively. Additional laboratory studies were performed if the subject deviated from the expected course of recovery.

Survival in this study was 7 days, at which point the animals were humanely euthanized under standard protocol, and necropsy was performed to extract the remaining kidney

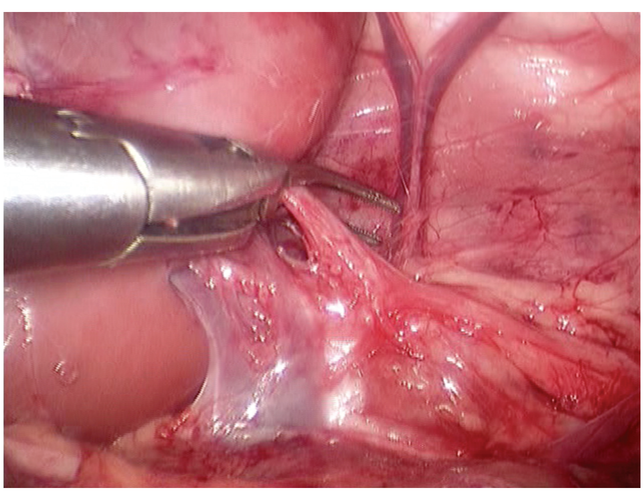

FIG. 1. The lower pole segmental artery is identified, isolated, and clamped.

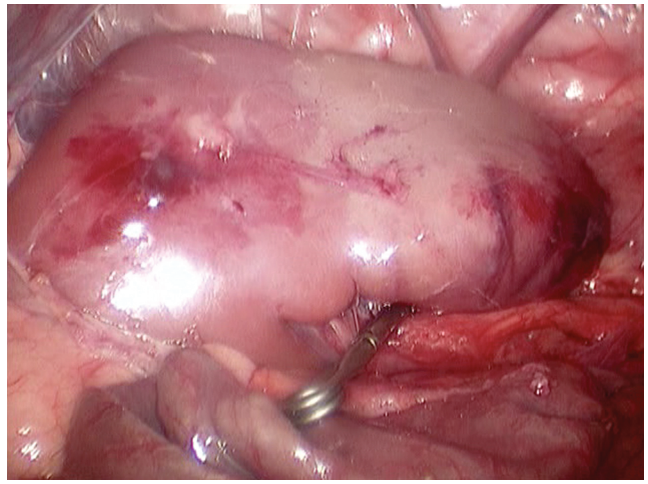

FIG. 2. After clamping, pallor of the lower pole is noted, with a clear line of demarcation between the lower pole and the remainder of the kidney, which remains perfused.

for pathologic analysis. In instances of clinical deterioration, renal failure (creatinine >8; potassium >6.5), or significant distress, the animal was euthanized before the 7-day survival period had expired, based upon recommendations from the supervising veterinarian.

The laboratory results at each time point were evaluated with a 2-way analysis of variance (ANOVA). When appropriate, *post hoc* analysis was performed with a modified Bonferroni posttest to elucidate the nature of the effects of intervention upon outcomes based upon laboratory data.

As no 7-day data were available for the 90-minute nonselective group because of factors described below, 2-way repeated-measures analysis could not be performed to comprehensively evaluate the laboratory data for the full 7-day time course of the study. As a surrogate measure, a one-way repeated measures ANOVA was performed for the 60-minute selective and nonselective, as well as the 90-minute nonselective group, and Tukey's Honestly Significant Difference (HSD) test was utilized for *post hoc* analysis. Unfortunately, this method did not allow for scrutiny of the interaction of effects of each intervention, though subset analysis evaluating the trajectory and mean absolute change of both blood urea nitrogen (BUN) and creatinine was able to elucidate some of the effects, albeit with an unknown degree of error.

Representative sections from the upper, middle, and lower-middle pole of each kidney were independently reviewed by a pathologist. Specimens were examined under low power to identify areas of hemorrhage and necrosis. In addition, each specimen was evaluated under higher power for evidence of glomerulosclerosis, tubular atrophy and necrosis, interstitial inflammation, and fibrosis, as well as vascular abnormality, including hypertrophy and thrombus. Each finding was graded on a scale ranging from 0 to 4, with 0 representing a negative finding and 4 representing severe and widespread involvement in the specimen examined.

Results

Demographics and perioperative data

There were no differences between the four groups with regard to subject weight (mean, 32.9 kg; $p = 0.07$) and kidney

size based upon radical nephrectomy specimens (mean, 98.6 g; $p = 0.4$), as well as preoperative BUN (mean, 9.7; $p = 0.8$) and creatinine (mean, 1.0; $p = 0.4$).

Across all subjects, an average of 10.8 g of renal parenchyma was resected (range, 9.0–13.4 g). There was no difference in the amount of tissue resected between the four experimental groups ($p = 0.718$). There were no intraoperative or immediate postoperative complications.

All subjects in both the 60- and 90-minute selective clamping groups as well as the 60-minute nonselective clamping group survived for 7 days without the need for supportive therapy. However, all subjects in the 90-minute nonselective clamping group experienced rapid deterioration to florid renal failure within the first 72 hours, meeting criteria for early euthanization.

Laboratory analysis

Baseline and postoperative laboratory data are summarized in Tables 1 and 2, as well as in Figure 3.

BUN and creatinine at 24 hours postoperatively. At 24 hours, there was no significant difference in BUN or creatinine between the 60-minute selective and nonselective groups, and the 90-minute selective group ($p > 0.05$). However, the BUN and creatinine for the 90-minute full-clamping group significantly differed from the remainder of the groups ($p < 0.0001$). For the 60-minute groups, the type of clamping (selective vs. nonselective) had no impact upon BUN or creatinine, while clamping type did demonstrate a profound impact upon BUN and creatinine in the 90-minute groups ($p < 0.0001$) (Fig. 4).

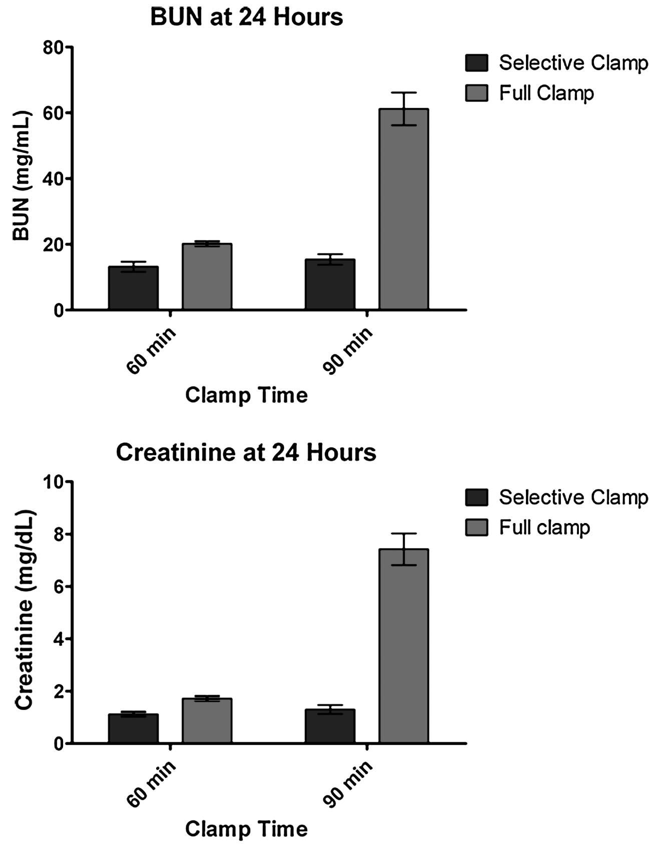

FIG. 4. BUN and creatinine at 24 hours postoperatively.

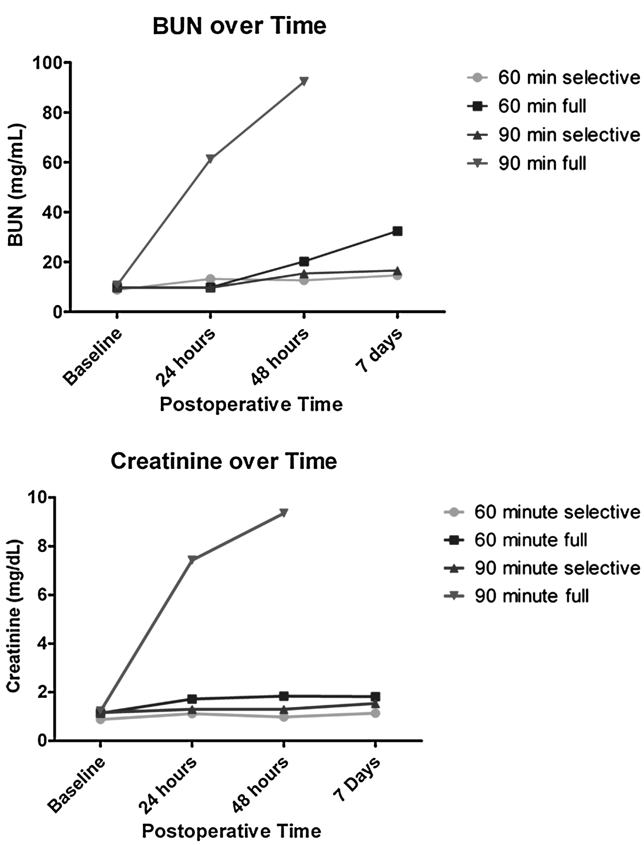

FIG. 3. Blood urea nitrogen (BUN) and creatinine over time.

BUN and creatinine at 48 hours postoperatively. At 48 hours postoperatively, the BUN and creatinine levels for the 90-minute full-clamping group significantly differed from the remaining three groups ($p < 0.0001$). Both 60-minute groups and the 90-minute selective clamping group demonstrated equivalent results for BUN and creatinine at 48 hours ($p > 0.05$). For the 90-minute group, clamping type had a significant impact upon both BUN and creatinine ($p < 0.0001$). (Fig. 5).

BUN and creatinine at 7 days postoperatively. For the 60-minute nonselective clamping group, BUN was significantly higher than both the 60- and 90-minute selective clamp groups ($p < 0.003$), while there was no statistical difference in BUN between the 60- and 90-minute selective clamp groups. As all 90-minute nonselective clamp subjects did not survive for the full 7 days, comparisons with that group cannot be made. For creatinine, the clamping type only impacted the 60-minute group ($p < 0.03$); however, there was no difference between 60- and 90-minute selective clamping, or 60-minute nonselective versus 90-minute selective clamping (Fig. 6).

Overall effects of clamping upon BUN and creatinine. An evaluation of the difference between baseline and BUN at 7 days reveals that BUN levels in all groups rose to a significant degree over the course of the study. However, when mean absolute changes in BUN are compared, there was no differ-

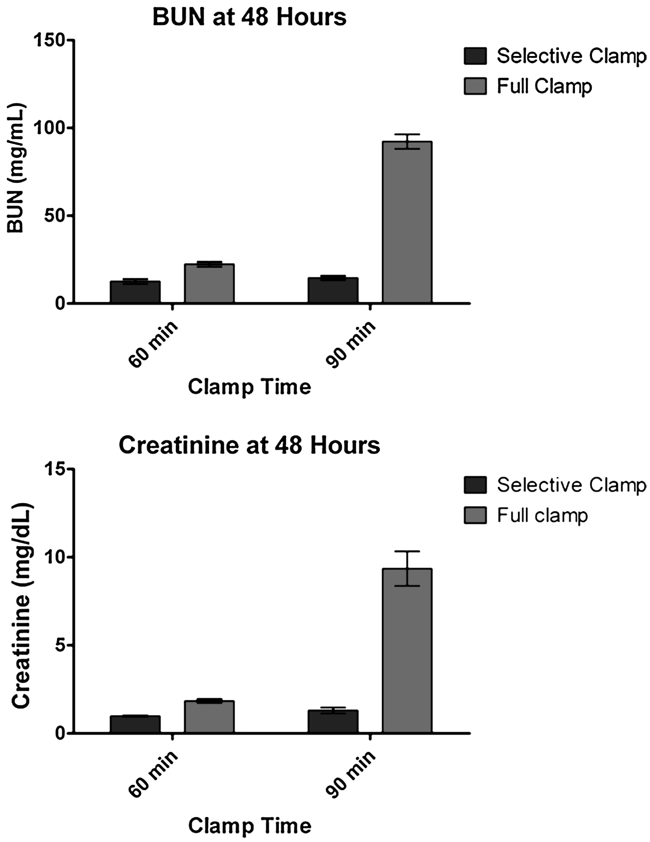

FIG. 5. BUN and creatinine at 48 hours postoperatively.

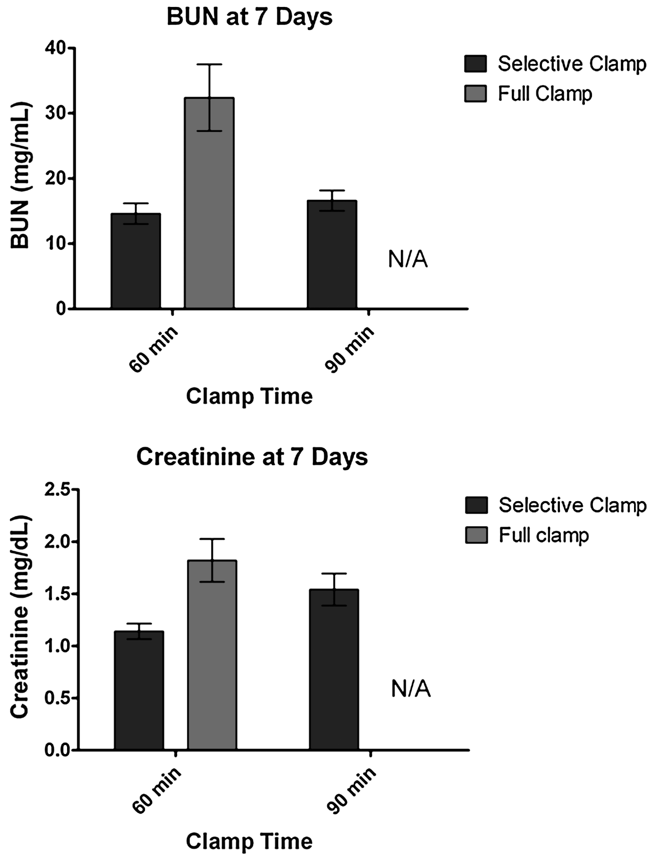

FIG. 6. BUN and creatinine at 7 days postoperatively.

ence in the change in BUN between the selective clamp groups, while nonselective clamping produced a significantly greater rise in BUN than selective clamping when compared to both the 60- and 90-minute selective clamping groups ($p = 0.008$). Creatinine significantly rose in the 60-minute full-clamping group (1.14 baseline vs. 1.82 at 7 days, $p = 0.02$), while no difference was observed in either of the selective clamping groups.

Pathologic analysis

Both the 60-minute selective and nonselective groups, as well as the 90-minute selective group demonstrated little overall change in cytoarchitecture. Interstitial inflammation was present throughout the majority of specimens, in both the ischemic and nonischemic portions of the selectively clamped kidneys; however, the severity of inflammation did not appear to correlate with either the type or duration of clamping. Grossly, simple vascular congestion was noted in most of the nonischemic tissue in the selective clamp series, while outright hemorrhage and necrosis was more often found in ischemic areas of both the selective and nonselective clamp specimens, especially in the 90-minute cohort.

Glomerulosclerosis, tubular dilation and atrophy, and tubular necrosis were rarely observed in the nonischemic portions of both of the selective clamp and the 60-minute nonselective specimens, but was noted extensively throughout the specimens who were subjected to 90 minutes of nonselective clamping. Overall, the pathologic evaluation correlates closely to the laboratory findings.

Discussion

Over the past two decades, partial nephrectomy has established itself as the treatment of choice for the management of low-stage renal malignancy. Boasting oncologic outcomes equivalent to radical nephrectomy,[4] while providing maximal preservation of functional renal reserve,[3,4] partial nephrectomy is now advocated for most patients with small renal masses, even those with normal contralateral kidneys.[13]

Laparoscopic partial nephrectomy has further refined nephron-sparing surgery, by providing equivalent oncologic control to open procedures, with the additional advantage of faster recovery times, owing to the avoidance of a morbid subcostal incision.[14–16]

One potential drawback to minimally invasive approaches for partial nephrectomy is the exposure of the kidney to the potentially deleterious effects of warm ischemia. Unlike open procedures, where the renal bed may be packed with ice, or local control can be exerted with manual compression, traditional laparoscopic approaches require arterial occlusion without the benefit of cooling. While a method for infusion of a cooling solution via intraarterial catheter has been described,[17] the technique is technically demanding, and requires vascular repair, thus extending the ischemic times.

Other methods aimed at reducing the extent and duration of warm ischemia have been described, including on-demand clamping,[11] early unclamping,[12] and selective arterial embolization.[10] Recently, Nohara et al.[18] described a technique for

selective renal artery clamping during open partial nephrectomy. The authors were successful in isolating a segmental renal artery in 40% to 60% of cases. At 1 week postoperatively, the authors found that patients who underwent selective renal artery clamping had a significantly lower increase in serum creatinine than those who underwent nonselective clamping (0.01 mg/dL vs. 0.15 mg/dL, respectively). However as their patients were subjected to cold ischemia from external ice-slush cooling, it is unclear how applicable these results are to warm ischemia that is typical of a laparoscopic approach.

To our knowledge, there has been no study to date that aims to evaluate the potential benefit of selective arterial clamping for laparoscopic partial nephrectomy, under the conditions of warm ischemia. To that end, we sought to evaluate the clinical and pathologic outcomes of selective versus nonselective renal artery control in a porcine model. We chose the setting of a solitary kidney to eliminate potential obfuscation of actual renal functional losses by a normal contralateral kidney.

Our present data suggest that selective arterial clamping may be beneficial in preventing loss of residual renal function in patients with limited renal reserve. Selective renal arterial clamping of both 60 and 90 minutes in the porcine model appears to preserve renal function in a manner superior to nonselective clamping. This advantage is subtle at 60 minutes, but proved critical to preserving function for ischemic times of 90 minutes.

The clamping times in our study may seem excessive, as they far exceed ischemic times that would be considered acceptable in human subjects. However, prior studies have clearly demonstrated that the porcine kidney is highly resilient, capable of recovering from 60 to120 minutes of warm ischemic insult.[19–22] As no direct comparison studies have been performed, it is unclear the manner in which ischemic times in the pig and human correlate. As such, we selected endpoints in our porcine model that we believed would best delineate transient and irrevocable renal parenchymal damage.

There are, however, limitations of our present study, and of the technique of selective arterial clamping in general, which warrant further discussion. Our sample size, with five subjects in each experimental group, is admittedly small. As a result, our data may be significantly underpowered. In addition, all pigs in the 90-minute nonselective clamping group experienced rapid clinical deterioration, meeting criteria for early euthanization. As such, we have no data for the 7-day endpoint in this group. From a practical standpoint, this prevented the comprehensive evaluation of the data with simple statistical analysis, requiring instead multiple subset analyses, all of which may contribute to additive error. However, as the differences noted in our analysis were all highly statistically significant, it is unlikely that type I error contributed significantly to our findings.

In addition, our endpoint for observation of 1 week may not have permitted each subject to fully recover from the insult of warm ischemia, and therefore the observed values for BUN and creatinine may not necessarily represent new baseline values. Unfortunately, the current model was not equipped to evaluate long-term renal function.

Further, our results are discordant with the findings of other authors who found that the porcine kidney was able to recover from ischemic times in excess of 90 minutes.[19–21] Most authors have noted a similar increase in mean serum creatinine levels at 48 hours, after which levels precipitously fall to near baseline.[19–21] However, it is critical to note that our study differs significantly from these prior studies in that we performed a partial nephrectomy in addition to vascular clamping; in the prior studies, only vascular clamping was performed. It is therefore possible that the additional insult of partial nephrectomy accounts for the divergence of our findings. Alternatively, our criteria for early euthanization based upon clinical status may account for these differences, as the subjects in question did not survive long enough to gauge for potential recovery of renal function as other authors have noted. As none of the prior studies reviewed commented on the clinical status of their subjects, it is difficult to make a direct comparison with our present experience. However, it must be noted that pathologic evaluation demonstrated areas of severe necrosis and tubular disruption in the 90-minute nonselective clamping group, findings that were not common in the other groups.

Technically, there are instances in which selective arterial clamping may not be feasible. In patients with dense or adherent perihilar fat, the delicate dissection required to isolate the segmental renal arteries may be impractically difficult. Likewise, short segmental arteries may not provide a wide enough berth to permit instrumentation for selective clamping. In addition, the delicate dissection required to skeletonize the renal hilum may carry with it significant morbidity, including vascular injury that may lead to significant hemorrhage or even loss of the renal unit. While we did not encounter any such difficulties in the porcine model, we acknowledge that there are critical anatomical differences in the human that may render selective control difficult, even in the hands of experienced surgeons. Indeed, even in one open model, successful selective clamping could only be accomplished in roughly half of all patients.[18]

In addition, one must consider practical applications of this technique based upon tumor location. Our present study focused upon the impact of selective lower pole segmental artery clamping, and therefore focuses on subjecting the kidney to a relatively small area of ischemia. It is unclear whether clamping of other segmental arteries, especially the posterior branch, which serves a relatively large portion of the renal parenchyma, would produce equivocal results. As such, further studies will need to be performed to determine the applicability of our results to tumor locations outside of the lower pole.

Conclusions

Selective arterial clamping is a safe and feasible means of vascular control during laparoscopic partial nephrectomy. In the porcine model, selective clamping appears to improve functional outcomes during prolonged periods of warm ischemic insult. Prospective evaluation of the technique in humans is necessary to determine if selective arterial control confers long-term functional benefits in patients with limited renal reserve.

Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

ANOVA = analysis of variance
BUN = blood urea nitrogen