**Grand Rounds**

**Functional Recovery From Prolonged Warm Ischemia: Compelling Case Scenarios**

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**CASE PRESENTATIONS**

**Index Case**

A 69-year-old man with a history of rheumatoid arthritis and pulmonary fibrosis presented with an incidentally discovered 11.5 cm left renal mass with a level 3 inferior vena cava (IVC) tumor thrombus, including involvement of the left adrenal and lumbar veins. The thrombus was highly vascularized as shown in Figure 1A-C. Preoperative evaluation was negative for metastatic disease and the serum creatinine (SCr) level was 1.55 mg/dL, correlating with an estimated glomerular filtration rate (eGFR) of 46 mL/min/1.73m². The patient was taken to the operating room for left radical nephrectomy, adrenalectomy, IVC thrombectomy, and retroperitoneal lymphadenectomy. In the recovery room, the patient was hemodynamically stable but was found to be anuric despite adequate fluid resuscitation. Renal ultrasound demonstrated no arterial flow in the right renal artery and flow to the parenchyma was also not observed. The patient was then taken for angiography which revealed complete occlusion of the main right renal artery approximately 2 cm distal to its origin, posterior to the IVC. Distal arterial flow beyond this region was not observed and attempts to advance a wire were unsuccessful (Fig. 1D). Aortogram did not demonstrate an accessory right renal artery and no arterial flow to the kidney were observed via collateral channels.

The patient was urgently brought back to the operating room for open exploration about 7-8 hours after the nephrectomy procedure was completed. A titanium clip was found to be occluding the right renal artery consistent with the findings on angiography. After obtaining proximal and distal control this clip was removed, a transverse arteriotomy was made at the site of occlusion, and a 1 cm thrombus was removed. After tacking the intimal flap caused by the clip, the arteriotomy was closed. The proximal and distal clamps were then removed and resumption of arterial flow to the kidney was observed. Intraoperative ultrasound confirmed improved intraparenchymal flow, which was entirely absent prior to this. Renal biopsy shortly after revascularization demonstrated fibrin deposition within the glomeruli as well as evidence for substantial ischemic injury. However, the majority of the tubules and glomeruli were still nucleated, demonstrating potential viability. Approximately 8-9 hours elapsed between closure of the nephrectomy procedure and revascularization.

The patient remained anuric for 4 days followed by 4 days of oliguria, and required dialysis for 3 weeks postoperatively, including 3 days of continuous renal replacement therapy followed by 8 intermittent hemodialysis sessions (Fig. 2 and Table 1). The final session of dialysis was administered on postoperative day 20. The SCr level fell to 3.2 mg/dL on postoperative day 50 and remained less than 3.0 mg/dL from that point forward. The patient’s nadir SCr was eventually noted to be 2.05 mg/dL approximately 2 years after surgery (Fig. 2). The patient died of metastatic kidney cancer shortly after this with stable renal function provided by the solitary right kidney. The final measured SCr level was 2.3 mg/dL.

**OTHER REPRESENTATIVE CASES**

Other cases in our experience also suggest sufficient and stable renal recovery after prolonged warm ischemia (Table 1). A 31-year-old testicular cancer patient presented after cisplatin-based chemotherapy with a 12 cm retroperitoneal mass that was encasing the aorta and
grossly involving the proximal left renal artery (Case 2). On imaging, no accessory left renal arteries were identified. The patient underwent retroperitoneal lymph node dissection with aortic resection and reconstruction with a synthetic graft. During this time, the left renal artery was disconnected from the aorta and eventually reconstructed and reimplanted into the graft. Additional arterial flow to the kidney was not identified despite extensive hilar dissection. In the interval, the left kidney experienced >90 minutes of warm ischemia. Hypothermia was not applied. Postoperatively, the SCr level peaked at 3.0 mg/dL but declined to 1.6 mg/dL at discharge, and remained stable at this level for many years. At 5-year follow-up, split renal function on nuclear renal scan showed 55% function in the revascularized left kidney. At 14-year follow-up, the SCr level remained stable at 1.5 mg/dL.

A healthy 64-year-old man with a 5.9 cm centrally located right renal mass underwent a challenging laparoscopic partial nephrectomy (PN) with complete hilar occlusion and a total warm ischemia time of 62 minutes (Case 3). Prior to surgery, the global eGFR was 74 mL/min/1.73m² with nuclear renal scan showing 44% function in the right kidney, corresponding with an eGFR of 33 mL/min/1.73m² specific to this kidney. One year after surgery, the global eGFR was 62 mL/min/1.73m² with split function of 34% in the right kidney, correlating with an eGFR of 21 mL/min/1.73m² within the operated kidney. Hence, 64% (21 of 33) of the function was preserved within the operated kidney exposed to ischemia. Direct measurement of the amount of vascularized parenchyma in the right kidney from the preoperative and postoperative CT scans demonstrated volumes of 145 cm³ and 78 cm³, respectively, corresponding with preservation of 54% of the vascularized nephron volume in the operated kidney. Hence, the data suggest that the preserved nephrons in the operated kidney exhibited complete recovery from the ischemic insult, even though the warm ischemia time was greater than 1 hour.

Finally, a 57-year-old man with a history of end-stage renal disease secondary to type 1 diabetes mellitus presented for simultaneous kidney/pancreas transplant from a deceased donor (Case 4). The renal allograft was implanted first without difficulty. Attention was then turned to the pancreatic transplant and the retractor blades were positioned to facilitate this. After completion of the vascular and enteric anastomoses, edema and congestion of the pancreas were observed due to portal venous thrombosis. Alternative venous outflow reconstruction was required. After this was completed, the retractor was relaxed and the renal allograft was again inspected and found to be ischemic. Doppler ultrasound revealed no detectable signal in the

**Figure 1.** Preoperative CT imaging and postoperative angiogram for index case 1. (A) CT abdomen and pelvis with intravenous contrast demonstrating an 11.5 cm infiltrative left renal mass on coronal image; (B) Enhancing tumor thrombus in IVC, left renal vein, and left adrenal vein; (C) Enhancing tumor thrombus extending into left lumbar vein; (D) Angiogram 6-7 hours after radical nephrectomy, IVC thrombectomy and RPLND showing catheter in right renal artery (arrow) and no contrast advancing beyond the metal clip (*). The aortogram did not demonstrate accessory renal arteries and no arterial flow to the right kidney was observed.
parenchyma despite attempts at repositioning. After obtaining proximal vascular control, a transverse arteriotomy was performed, and a large intraluminal clot was removed. Return of flow was confirmed and the arteriotomy was repaired and closed. Warm ischemia time for the kidney was estimated to be greater than 90 minutes given that the pancreatic transplant took approximately 2 hours and the retractor blades placed at the beginning of this appeared to be the cause of the ischemia. The patient had delayed graft function with a peak SCr level of 4.66 mg/dL on postoperative day 11. Dialysis was not required. Transplant renal ultrasound confirmed patency of the renal vasculature and nuclear renal scan on postoperative day 10 was consistent with acute tubular necrosis. By 3 weeks after surgery, the SCr level fell to 2.0 mg/dL then reached a nadir of 1.45 mg/dL where it remains 3 years after transplant.

**DISCUSSION BY STEVEN C. CAMPBELL, MD**

Presented by Steven C. Campbell, M.D., Ph.D

Recovery of renal function after exposure to ischemia is a common concern after clamped PN for renal malignancy but can also be an important consideration for renal transplant recipients, after trauma to the renal hilum, or when associated with complex vascular or reconstructive procedures involving the kidney. The degree of functional recovery is of greatest clinical relevance when the entire parenchymal volume has been exposed to the ischemic insult (eg, patients with a solitary kidney) or when functional reserve is compromised prior to the event. Patients with pre-existing chronic kidney disease (CKD) or those with anatomic or functional abnormalities affecting the contralateral kidney fall into the latter category. In all of these settings, incomplete recovery from the ischemic insult can place the patient at risk for acute kidney injury (AKI) and progressive CKD.

Most data suggest that hypothermia is strongly protective against irreversible nephron injury and remains protective for several hours. After clamped PN performed with hypothermia, median recovery of renal function in the operated kidney is 99% of that expected by parenchymal mass preservation, and remains greater than 95% even when the ischemia time is greater than 35 minutes. Hypothermia is also routinely utilized for renal transplants where ischemia times can extend to several hours without precluding near complete recovery of function. AKI can occur with exposure to any form of ischemia, although it tends to be short-lived and substantial recovery is typically observed. After PN, prolonged hypothermia can be associated with AKI, but most such kidneys eventually recover to greater than 85%-90% of the functional level predicted by nephron mass preservation, even with high grade

![Figure 2. Postoperative renal function for index case 1, including serum creatinine levels and daily urine outputs from the remaining solitary right kidney. The patient was anuric for 4 days after surgery and underwent 3 days of continuous renal replacement therapy followed by 8 sessions of intermittent hemodialysis as indicated.](image-url)
### Table 1. Cases with Prolonged Warm Ischemia and Analysis of Functional Recovery.

<table>
<thead>
<tr>
<th>Case</th>
<th>Oncologic Surgery with Iatrogenic Trauma to Renal Artery</th>
<th>Oncologic Surgery Requiring Renal Revascularization</th>
<th>Clamped PN with Prolonged Warm Ischemia</th>
<th>Renal Transplant with Prolonged Warm Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and comorbidities</td>
<td>69-year-old male, Rheumatoid arthritis, pulmonary fibrosis</td>
<td>31-year-old male, Stage 2C testis cancer, residual mass after BEPx4</td>
<td>64-year-old male, Healthy</td>
<td>57-year-old male, Type 1 diabetes, end stage renal failure</td>
</tr>
<tr>
<td>Surgery</td>
<td>L radical nephrectomy, IVC thrombectomy, RPLND</td>
<td>RPLND, aortic resection above level of L renal artery, reimplantation of L renal artery into vascular graft</td>
<td>Laparoscopic right PN</td>
<td>Simultaneous renal/pancreas transplant</td>
</tr>
<tr>
<td>Relevant preoperative information</td>
<td>cT3c, 11.5 cm L renal mass with hypervascular level 3 IVC thrombus</td>
<td>12 × 11 cm postchemotherapy mass encasing aorta and origin of L renal artery</td>
<td>cT1b, 5.9 cm renal mass, Central tumor location R.E.N.A.L. = 9</td>
<td>Dialysis dependent and endocrine pancreatic insufficiency</td>
</tr>
<tr>
<td>Pathology</td>
<td>pT4 N1, grade 3, clear cell RCC</td>
<td>Fibrosis and teratoma, no viable cancer</td>
<td>pT1b, grade 2, clear cell RCC</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Warm ischemia time</td>
<td>8-9 hours, as proven by aortogram showing no flow to R kidney. Patient also had complete anuria, and US showed no arterial flow within the R kidney</td>
<td>Approximately 90 minutes. L kidney was completely dissected free of aorta and then the renal artery was reconstructed and re-implanted into the aortic graft. Hypothermia was not applied.</td>
<td>62 minutes total, with complete hilar occlusion. Hypothermia was not applied.</td>
<td>Greater than 90 minutes (occurred during complex pancreatic transplant and remained ischemic until the renal transplant was revascularized). Hypothermia was not applied.</td>
</tr>
<tr>
<td>Preoperative functional characteristics</td>
<td>SCr 1.55, eGFR 46, Poor function L kidney</td>
<td>Normal renal function</td>
<td>eGFR 74, L56%, R44%*</td>
<td>End-stage renal failure</td>
</tr>
<tr>
<td>Early postoperative kidney function</td>
<td>AKI with anuria for 4 days</td>
<td>Postoperative AKI with peak SCr 3.0</td>
<td>AKI was not observed</td>
<td>Postoperative AKI with peak SCr 4.7</td>
</tr>
<tr>
<td>Dialysis needed</td>
<td>Yes (for 3 weeks)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Long-term functional outcome</td>
<td>At 2 years: SCr 2.0, eGFR 34</td>
<td>At 5 years: SCr 1.5, L55%, R45%*</td>
<td>At 1 year: eGFR 62, L66%, R34%*</td>
<td>At 3 years: SCr 1.5</td>
</tr>
<tr>
<td>Long-term outcome</td>
<td>Death from metastatic RCC; final SCr 2.3</td>
<td>Alive, cancer-free, good recovery of L kidney</td>
<td>Alive, cancer-free, stable renal function</td>
<td>Alive, stable renal function</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; BEP, bleomycin, etoposide, and cisplatin chemotherapy; eGFR, estimated glomerular filtration rate (ml/min/1.73 m²); IVC, inferior vena cava; L, left; PN, partial nephrectomy; R, right; RCC, renal cell carcinoma; R.E.N.A.L., (R)adius (tumor size as maximal diameter), (E)xophytic/endophytic properties of tumor, (N)earness of tumor deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to polar lines; RPLND, retroperitoneal lymph node dissection; SCr, serum creatinine level (mg/dL); US, ultrasound.

* MAG-3 nuclear renal scan for relative renal function.
AKI. Such kidneys tend to retain stable renal function subsequent to this for a number of years, as long as impactful comorbidities (eg, diabetes) do not intervene.

Data about warm ischemia and its relationship to irreversible ischemic injury is less definitive, although most studies suggest that limited durations of warm ischemia are well tolerated. After clamped PN utilizing limited warm ischemia, the median recovery of renal function in the operated kidney is 90%-95% of that expected by parenchymal mass preservation, and it falls about 3% from this level with each additional 10-minute interval of warm ischemia, at least out to 40-45 minutes. Hence, the average kidney exposed to 45 minutes of warm ischemia will eventually recover to about 80%-84% of what would be expected by nephron mass preservation alone. It should be noted that this is the average recovery, with some kidneys failing to recover to this degree and others recovering more fully. In general, recovery from cold ischemia appears to be more consistent and reliable than recovery from warm ischemia.

Recovery from more prolonged intervals of warm ischemia is not well-studied, as most complex PN cases have traditionally been performed with hypothermia or zero or segmental ischemia techniques. Aortic reconstruction for severe vascular disease occasionally requires clamping above the renal arteries and reimplantation into the aorta, typically without hypothermia, similar to what was performed in case 2 of this series. Most such patients have experienced near complete functional recovery with avoidance of dialysis, both short- and long-term. The exact intervals of warm ischemia are not well-defined in some of these series, but many are likely greater than 45-60 minutes, and in case 2 of our series the warm ischemic interval was greater than 90 minutes.

Our cases suggest that a substantial degree of functional recovery may be possible even with prolonged warm ischemia, at least in occasional cases. While it is possible that collateral arterial supply may have been present in our cases, the clinical data suggests otherwise, particularly in our index case, where anuria was complete and the ultrasound and aortogram failed to demonstrate any arterial flow. In our second case, extensive hilar dissection was required essentially leaving the kidney only attached by the renal vein, and the preoperative and postoperative imaging did not demonstrate accessory arteries. In case 3, extensive hilar dissection was followed by en bloc hilar cross-clamping which incorporated all the venous outflow. Troublesome bleeding was not observed during cross-clamping, suggesting that an unrecognized and incompletely clamped accessory or branch artery was not present. In case 4, there was only 1 artery, the entire kidney was ischemic, and complete occlusion of the artery was found when arteriotomy was made. Nevertheless, although the possibility of collateral arterial inflow cannot be absolutely excluded in our 4 cases, it would be extremely unlikely given the above considerations.

Provocative studies by Parekh et al also suggest that recovery from extended warm ischemia may be more substantial than previously thought, at least in some patients. The authors prospectively studied 27 patients managed with PN utilizing warm ischemia with mean duration of 32 minutes and range up to 53 minutes. No substantial differences were observed when comparing mean postoperative and preoperative SCr levels, suggesting near complete recovery in most patients, and functional recovery did not correlate with duration of ischemia. Biopsies taken at various intervals failed to demonstrate histologic changes suggestive of ischemic injury, and biomarkers specific for injury to renal tubular cells failed to reveal evidence of substantial ischemic effect.

There are a number of potential explanations for the negative findings in this study, including methodological concerns. The biomarkers and intervals of testing chosen for the study may have not been optimal, and acute histologic findings may not necessarily correlate with irreversible ischemic injury. Nevertheless, the functional results are most interesting, and support the authors’ main thesis, although further research will be required.

Our cases were derived from 3 different centers over a 20-year period and were selected because they provide striking examples of functional recovery from extended warm ischemia. However, the denominator of cases managed with extended warm ischemia at our centers over this time period is not known, leaving the possibility that our findings may be anecdotal and perhaps not representative of functional outcomes in such settings. Data about functional recovery from prolonged warm ischemia remains limited, so our general approach has been to avoid extended warm ischemia during PN whenever feasible. Nevertheless, our study has potential clinical implications as it suggests that some kidneys exposed to extended warm ischemia may recover with revascularization, which may be a consideration in occasional patients with trauma to the renal hilum, particularly if a solitary kidney is present.

For PN, our current approach is to prioritize hypothermia whenever the ischemic interval may be greater than 30-40 minutes, particularly if the patient has a solitary kidney or pre-existing CKD. The American Urological Association guidelines recommends avoidance of prolonged warm ischemia during PN through the use of hypothermia or zero or segmental ischemia approaches, along with dedicated efforts to optimize nephron mass preservation. Hypothermia will remain the standard of care for renal transplantation and can also be considered in reconstructive surgery whenever prolonged ischemic intervals are anticipated. Further research into the functional impact of prolonged warm ischemia would be of great clinical utility, including elucidation of patient-related factors that might modify recovery in various circumstances.

References


