WARMING UP TO ISCHEMIA

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WHAT ARE THE GOALS OF A PARTIAL NEPHRECTOMY FOR RCC?

- **Primary** – Oncologic Efficacy
- **Secondary**
  - Preserve Renal Function
  - Reduce Perioperative morbidity
  - Cosmesis
Why is renal function important?
RENAL FUNCTION

• 25% with localized RCC undergoing surgery have pre-existing CKD even with normal serum creatinine

• 20% of patients undergoing PN will manifest CKD-III within 5 years of surgery

• 50-60% of patients undergoing will develop CKD-III within 5 years of surgery

Decreasing GFR correlated with risk of death, CVS events, and hospitalization
PREVENTIVE MEASURES

• Pre-operative evaluation
  • Identify proteinuria, hypertension, hyperlipidemia and reduced eGFR
  • Early referral to a Nephrologist has been shown to reduce mortality in a cohort of diabetic patients with CKD

• Use of renoprotective agents has not shown any benefit
Survival benefit of nephrological care

1997-2000

n= 39031 pts w/ DM and CKD III/IV

Mortality risk to # visits

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>2 visits</td>
<td>0.80</td>
<td>0.67-0.97</td>
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<tr>
<td>3 visits</td>
<td>0.68</td>
<td>0.55-0.86</td>
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<tr>
<td>4 visits</td>
<td>0.45</td>
<td>0.32-0.63</td>
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THE BEST WAY TO PRESERVE RENAL FUNCTION

Nephron sparing surgery
BASELINE RENAL FUNCTION

• Quality of baseline renal parenchyma sets the ceiling for post-operative recovery

• Major predictor of post-operative acute renal failure (ARF) and ESRD after PN

• Pre-operative eGFR is an independent predictor of:
  • Significant decrease in eGFR in solitary kidneys
  • Differential contribution of the operated organ in the presence of bilateral functioning kidneys
RENAL PARENCHYMAL VOLUME AFTER PN

- Percentage of preserved parenchyma is a significant and independent predictor of ultimate global renal function and function of the affected kidney

- Strong correlation - volume of parenchyma removed, surgical complexity and WIT

- 5% increase in the amount of kidney preserved correlates with 17% reduction in risk of post-operative de novo CKD-IV
Case 1

63 year female
Serum creatinine 0.7
No co-morbidities
Warm Ischemia Time
20 minutes
Case 2

70 year female
Serum creatinine 1.2
H/O DM, HTN, well controlled
Warm Ischemia Time

32 minutes
Warm Ischemia Time 20 min versus 32 min

Important ?
RENAL ISCHEMIA

• How reliable is the evidence that limited ischemia is unsafe?

• "It ain’t what you don’t know that gets you into trouble, It’s what you know for sure that just ain’t so" – Mark Twain
Renal Hypothermia: In Vivo and Ex Vivo

Andrew C. Novick, M.D.*

Temporary occlusion of the renal artery may be necessary for operations to remove renal calculi in situ, such as partial nephrectomy, nephrolithotomy, and extended pyelolithotomy. In such patients, temporary arterial occlusion not only diminishes intraoperative renal hemorrhage but also improves access to the intrarenal collecting system by causing the kidney to contract and reducing renal tissue turgor. Performance of these operations requires an understanding of renal responses to warm ischemia and available methods of protecting the kidney in situ when the period of arterial occlusion exceeds that which may be safely tolerated. Methods of extracorporeal renal preservation are also reviewed herein since autotransplantation and bench surgery may occasionally be employed to treat patients with renal calculous disease.

RENAL TOLERANCE TO WARM ISCHEMIA

to nucleoside and purine derivatives during episodes of renal ischemia. When energy sources have been depleted, cellular membrane transport mechanisms fail, causing an influx of salt and water, which ultimately results in severe cellular edema and cell death.

The extent of renal damage following normothermic arterial occlusion depends on the duration of the ischemic insult. Canine studies have shown that warm ischemic intervals of up to 30 minutes can be sustained with eventual full recovery of renal function. For periods of warm ischemia beyond 30 minutes, there is generally significant immediate functional loss while late recovery of renal function is either incomplete or absent (Table 1). Histologically, renal ischemia is most damaging to the proximal tubular cells, which may show varying degrees of necrosis and regeneration, while the glomeruli and blood vessels are generally spared.

Human tolerance to warm renal ischemia very closely parallels experimental canine observations, and in general 30 minutes is the maximum tolerable period of arterial occlusion before renal ischemic injury occurs. In spite of prompt reperfusion, functional return of the renal parenchyma is incomplete, and in the absence of additional insults, there is a progression from proximal tubular necrosis to interstitial fibrosis. Renal tolerance to warm ischemia is highest in the newborn and lowest in the geriatric kidney. The mechanism of cell death following warm ischemia is highly active, and it may be that this process is initiated and accelerated by the ischemic insult itself. The mechanisms of cellular death after ischemia are complex, and the relative contributions of necrosis, apoptosis, and autophagy are not yet fully understood.
### Uric Acid

Table 1. Tolerance of Unprotected Canine Kidney to Warm Ischemia

<table>
<thead>
<tr>
<th>Period of Warm Ischemia (Min)</th>
<th>Immediate Renal Functional Loss (%)</th>
<th>Recovery of Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Minimal</td>
<td>Complete, within minutes</td>
</tr>
<tr>
<td>20</td>
<td>40–50</td>
<td>Complete, within hours</td>
</tr>
<tr>
<td>30</td>
<td>60–70</td>
<td>Complete, 3 to 9 days</td>
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<tr>
<td>60</td>
<td>70–80</td>
<td>Usually, complete, weeks</td>
</tr>
<tr>
<td>120</td>
<td>100</td>
<td>Incomplete (30 to 50%)</td>
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<tr>
<td>180</td>
<td>100</td>
<td>None</td>
</tr>
</tbody>
</table>

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Determination of the Optimum Temperature for Regional Renal Hypothermia during Temporary Renal Ischaemia

J. P. WARD
Department of Urology, St Bartholomew's Hospital, London.

Summary

To determine the optimum temperature at which the in situ kidney should be maintained while it is ischaemic, 47 mongrel dogs were studied.

35 of these underwent 90 minutes of left renal ischaemia with the kidney temperature maintained at 37°, 30°, 22°, 15°, 10°, 5° and 0°C respectively.

The effect on renal function was determined by measurements of G.F.R. before and at regular 15-minute intervals after the ischaemic period. Computer statistical analysis exposed the optimum temperature to be 15°C.

Renal artery blood flow, renal histology, 51Cr labelled platelets and renal arteriography were used to determine the mechanism of ischaemic injury.

Quantitation of renal cell injury confirmed that no additional protection to ischaemia could be gained by cooling below 15°C.

15°C is recommended as the optimum temperature for use in clinical renal hypothermia.
With the information just provided, should we have accepted it as gospel?
• 362 pts undergoing PN in solitary kidneys from Mayo Clinic and Cleveland Clinic from 1990-2008

• WIT as a continuous variable found to be an independent predictor of adverse renal functional outcomes – *Therefore every single minute of WIT adds to the damage and counts!*

• WIT of 25 min proposed as a new safe cut off

Eur Urol, 2010
• 362 pts undergoing PN in solitary kidneys from Mayo Clinic and Cleveland Clinic from 1990-2008

• WIT as a continuous variable did not significantly associate with long term renal function after adjusting for quality and quantity of remnant renal parenchyma

• *Every single minute does not count!*
From 1980-2009, 660 pts undergoing PN in a solitary kidneys from 4 institutions

Ischemia Time was NOT an independent predictor of ultimate renal function after PN

Quantity and Quality of remnant renal parenchyma was more important

J Urol, Feb 2011
The flaw of retrospective studies, selection and investigator biases and

*not knowing what we don’t know*
What do all the previous articles prove?

Sanity is not statistical

George Orwell, 1948
exclusion of duplicates and papers with topics that were not specific for this review, we identified a list of 197 papers. The full text of these articles was assessed by two independent reviewers. Level of evidence, sample size, study design, and relevance of each study with regard to the topics of the review were assessed. Based on these criteria, 91 articles were selected with the consensus of all authors and were critically analyzed. The review is the result of an interactive peer-reviewing process by the expert panel.
“Consensus: “The process of abandoning all beliefs, principles, values, and policies in search of something in which no one believes, but to which no one objects; the process of avoiding the very issues that have to be solved, merely because you cannot get agreement on the way ahead. What great cause would have been fought and won under the banner: ‘I stand for consensus?’”

Margaret Thatcher
RENAL ISCHEMIA AND FUNCTION AFTER PARTIAL NEPHRECTOMY: A COLLABORATIVE REVIEW OF THE LITERATURE

Alessandro Volpe, Michael L. Blute, Vincenzo Ficarra, Inderbir S. Gill, Alexander Kutikov, Francesco Porpiglia, Craig Rogers, Karim A. Touijer, Hendrik Van Poppel, R. Houston Thompson

Table 1 - Recent studies on renal ischemia during partial nephrectomy in solitary kidneys

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, no.</th>
<th>Surgical approach</th>
<th>Aim of the study</th>
<th>Ischemia time, min</th>
<th>Tumor size, cm</th>
<th>Main outcomes</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson et al [33]</td>
<td>537</td>
<td>OPN</td>
<td>To compare renal complications among patients who underwent no ischemia (n = 85), WM (n = 174), and CI (n = 278)</td>
<td>6 vs 22 vs 45</td>
<td>2.5 vs 3.5 vs 4</td>
<td>WI and CI were associated with a significantly increased risk of acute and chronic renal failure and temporary dialysis compared to no ischemia. WIT &gt; 20 min and CIT &gt; 35 min were associated with a higher incidence of acute renal failure. WIT &gt; 20 min was associated with an increased risk of chronic renal failure and permanent dialysis.</td>
<td>3</td>
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<tr>
<td>Thompson et al [34]</td>
<td>362</td>
<td>OPN (n = 319)</td>
<td>To assess the association of WIT with postoperative and long-term RF</td>
<td>Median: 21 (range: 4-55)</td>
<td>Median: 3.4 (range: 0.7-18)</td>
<td>Longer WIT was associated with acute renal failure, a GFR &lt; 15 mL/min in the postoperative period, and with new-onset stage 4 CKD during follow-up. A WIT cut point of 25 min provided the best distinction between patients with and without these endpoints.</td>
<td>4</td>
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<tr>
<td>Lane et al [35]</td>
<td>660</td>
<td>OPN</td>
<td>To compare the impact of WI (n = 360) and CI (n = 300) on RF</td>
<td>WI median: 22 (IQR: 17-27)</td>
<td>CI median: 45 (IQR: 35-60)</td>
<td>Median GFR decreased similarly 3 mo after surgery with CI or WI. Percentage of parenchyma spared and preoperative GFR were the only primary determinants of ultimate RF at multivariable analysis.</td>
<td>3</td>
</tr>
<tr>
<td>Thompson et al [35]</td>
<td>362</td>
<td>OPN</td>
<td>To evaluate the effects of WIT and quantity and quality of kidney preserved on recovery of RF after surgery</td>
<td>Median: 21 (range: 4-55)</td>
<td>Median: 3.4 (range: 0.7-18)</td>
<td>Median GFR decreased similarly 3 mo after surgery with CI or WI. Percentage of parenchyma spared and preoperative GFR were the only primary determinants of ultimate RF at multivariable analysis.</td>
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</tr>
<tr>
<td>Lane et al [15]</td>
<td>199</td>
<td>OPN</td>
<td>To compare RF outcomes of OPN and LPN and assess predictors of postoperative RF</td>
<td>0-21 (IQR: 17-27)</td>
<td>3.8 (IQR: 2.8-4.8)</td>
<td>WIT was significantly longer with LPN, WIT, age, preoperative eGFR, but not surgical approach, were independently associated with poorer postoperative eGFR at multivariate analysis.</td>
<td>3</td>
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</tbody>
</table>

Cl = cold ischemia; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IQR = interquartile range; LPN = laparoscopic partial nephrectomy; OPN = open partial nephrectomy; RF = renal function; WI = warm ischemia; WIT = warm ischemia time.

* Assessment of preoperative renal function was included in the analysis of predictors of postoperative renal functional outcomes.

‡ Assessment of the amount of preserved/resected renal parenchyma was included in the analysis of predictors of postoperative renal functional outcomes.
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<th>Study</th>
<th>Patients, no.</th>
<th>Surgical approach</th>
<th>Aim of the study</th>
<th>Ischemia time, min</th>
<th>Tumor size, cm</th>
<th>Nephrometry score (mean)</th>
<th>Main outcomes</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson et al [48]</td>
<td>PN with WI (n = 362)</td>
<td>OPN (n = 411)</td>
<td>To compare the short- and long-term renal effects of WI vs no ischemia in patients with a solitary kidney</td>
<td>Median: 21</td>
<td>Mean: 3.4</td>
<td>Mean: 2.5</td>
<td>Patients who underwent WI were significantly more likely to develop acute renal failure, a GFR &lt;15 ml/min per 1.73 m² in the postoperative period, and new-onset stage 4 CKD during follow-up.</td>
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<td>PN with no ischemia (n = 96)</td>
<td>LPN (n = 47)</td>
<td></td>
<td>(range: 4–55)</td>
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<td>Kopp et al [49]</td>
<td>Clamped PN (n = 164)</td>
<td>OPN</td>
<td>To analyze factors affecting postoperative RF using both the clamped and clamped warm ischemic technique</td>
<td>Mean: 24.50</td>
<td>Median: 3.5</td>
<td>Median: 4.0</td>
<td>De novo stage 3 CKD at last follow-up was more frequent after clamped vs clamped PN. Increasing WIT was an independent predictor of stage 3 CKD after clamped PN.</td>
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<td>Clamless PN (n = 64)</td>
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<tr>
<td>Smith et al [50]</td>
<td>Clamped PN (n = 116)</td>
<td>OPN</td>
<td>To determine safety and impact on RF of clamped PN</td>
<td>Mean: 20</td>
<td>Median: 3.0</td>
<td>Median: 2.8</td>
<td>The % eGFR change at 1 yr was overall similar for the clamped and unclamped group (p = 0.037), but not in patients with solitary kidneys (21% vs 4.4%; p = 0.027). The rate of complications was similar in the groups.</td>
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<td>Clamless PN (n = 192)</td>
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<tr>
<td>Kaczmarek et al [52]</td>
<td>Clamped PN (n = 49)</td>
<td>RAPN</td>
<td>To evaluate the functional outcomes of RAPN with and without hilar clamping in a propensity score matched analysis</td>
<td>Mean: 18.50</td>
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<td>Off-clamp RAPN had a significantly shorter operative time, higher EBL, and smaller decrease in eGFR compared to clamped RAPN.</td>
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<td>Clamless PN (n = 283)</td>
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<tr>
<td>Porpiglia et al [53]</td>
<td>Clamped PN (n = 44)</td>
<td>LPN</td>
<td>To compare postoperative RF of clamped vs clamped LPN (WIT &lt;25 min) by using renal scintigraphy</td>
<td>Mean: 18</td>
<td>Mean: 3.4 ± 1.1</td>
<td>Mean: 3.6 ± 1.4</td>
<td>RF loss assessed by renal scan was not significantly different 3 mo after clamped and clamped LPN. Patients with poor preoperative RF had the most benefit with a clamped approach.</td>
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<td>Clamless PN (n = 42)</td>
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<tr>
<td>Gill et al [54]</td>
<td>Zero ischemia (n = 58)</td>
<td>LPN (n = 43)</td>
<td>To present the concept and assess the perioperative outcomes of zero ischemia PN</td>
<td>0</td>
<td>Mean: 3.2</td>
<td>7 ± 1.9</td>
<td>RF loss assessed by renal scan was not significantly different 3 mo after clamped and clamped LPN. Patients with poor preoperative RF had the most benefit with a clamped approach.</td>
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<td>RAPN</td>
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<tr>
<td>Ng et al [55]</td>
<td>Zero ischemia with VMD (n = 22)</td>
<td>LPN or RAPN</td>
<td>To evaluate whether VMD of renal artery branches allows zero ischemia PN to be performed even for challenging medial tumors</td>
<td>0</td>
<td>Mean: 4.3 ± 2.6</td>
<td>Mean: 2.6 ± 1.0</td>
<td>Perioperative outcomes were similar in the two groups. The median serum creatinine level was similar 2 mo postoperatively.</td>
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<td>Zero ischemia without VMD (n = 22)</td>
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<tr>
<td>Shao et al [58]</td>
<td>Segmental artery clamping (n = 44)</td>
<td>LPN</td>
<td>To evaluate the feasibility and efficiency of LPN with segmental renal artery clamping in comparison with the conventional technique</td>
<td>Mean: 22 ± 4.4</td>
<td>Mean: 3.5 ± 0.4</td>
<td>Mean: 3.4 ± 0.5</td>
<td>LPN with segmental artery clamping improves early postoperative RF compared with main renal artery clamping.</td>
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<td>Main artery clamping (n = 31)</td>
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<td>Study</td>
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<td>Ischemia time, min</td>
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<tr>
<td>Popigia et al [37]</td>
<td>18</td>
<td>LPN with WIT &gt; 30 min</td>
<td>To evaluate the impairment of RF of the operated kidney 12 mo after surgery by using renal scans (preoperative; 5 d, 3 mo, and 6 mo postoperative)</td>
<td>Mean: 39 ± 8.1</td>
<td>Mean: 3.4 ± 1.8</td>
<td>Kidney damage occurs during LPN when WIT &gt; 30 min and is only partially reversible. The functional impairment of the operated kidney is significantly worse with WIT &gt; 32 min. Preoperative RF and percent of functional volume preservation are the primary determinants of long-term functional outcomes in patients with normal preoperative RF who have ischemia time within acceptable limits.</td>
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<td>Simmons et al [4]</td>
<td>39</td>
<td>OPN/LPN</td>
<td>To assess a novel method to estimate the percent of functional volume preservation and to assess its effect on postoperative functional outcomes.</td>
<td>Median CIT: 38.5</td>
<td>Median 3.5</td>
<td>Preoperative RF and percent of functional volume preservation are the primary determinants of long-term functional outcomes in patients with normal preoperative RF and ischemia time within acceptable limits.</td>
<td>4</td>
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<tr>
<td>Parekh et al [3]</td>
<td>40</td>
<td>OPN</td>
<td>To prospectively assess the renal response to clamp ischemia and reperfusion after PN, including histologic changes on biopsies performed before, during, and after clamping, and changes in biomarkers of acute kidney injury.</td>
<td>Mean CIT: 48</td>
<td>Mean WIT: 32.3</td>
<td>RF changes did not correlate with ischemia duration. Renal structural changes were much less severe than observed in animal models that used similar duration of ischemia. Acute kidney injury biomarkers were only mildly elevated and did not correlate with or extend duration of ischemia.</td>
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<tr>
<td>Shikanov et al [87]</td>
<td>401</td>
<td>LPN</td>
<td>To assess the influence of renal ischemia on long-term global RF assessed with eGFR.</td>
<td>Median WIT: 29</td>
<td>Median: 2.5</td>
<td>WIT did not have a clinically significant impact on global RF after LPN. WIT and endophytic tumor location are associated with a statistically significant loss of differential RF, but only in the group who experienced a WIT &gt; 30 min.</td>
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<tr>
<td>Pouliot et al [38]</td>
<td>56</td>
<td>LPN</td>
<td>To evaluate the effect of WIT and other factors on differential RF of the operated kidney assessed by using renal scans (preoperative; 10 d postoperative).</td>
<td>Mean: 30 ± 9</td>
<td>Mean: 3.2 ± 1.6</td>
<td>While total RF is almost unaffected after surgery, a WIT &gt; 25 min leads to a significant decrease in effective renal plasma flow on the operated side. WIT as a continuous variable is associated with greater loss of RF. ROC analysis identifies 25 min as a soft WIT cut off. Loss of RF occurs within 3 mo and remains stable until 12 mo after LPN. Intraperitone, visually estimated preserved parenchyma volume, radiologic tumor size, and procedure type significantly correlate with postoperative unilateral RF at univariable analysis. No factor is an independent predictor at multivariable analysis.</td>
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<tr>
<td>Funahashi et al [40]</td>
<td>32</td>
<td>OPN (n = 20) LPN (n = 2012)</td>
<td>To evaluate the differential RF of the operated kidney by using renal scans (preoperative; 1 wk and 6 mo postoperative).</td>
<td>OPN: 24.2 ± 6.2</td>
<td>OPN: 2.5 ± 0.6</td>
<td>While total RF is almost unaffected after surgery, a WIT &gt; 25 min leads to a significant decrease in effective renal plasma flow on the operated side. WIT as a continuous variable is associated with greater loss of RF. ROC analysis identifies 25 min as a soft WIT cut off. Loss of RF occurs within 3 mo and remains stable until 12 mo after LPN. Intraperitone, visually estimated preserved parenchyma volume, radiologic tumor size, and procedure type significantly correlate with postoperative unilateral RF at univariable analysis. No factor is an independent predictor at multivariable analysis.</td>
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<td></td>
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<tr>
<td>Popigia et al [39]</td>
<td>53</td>
<td>LPN</td>
<td>To assess the effects of WIT on RF after LPN in patients with a normal contralateral kidney by using renal scans (preoperative; 3 and 6 mo postoperative).</td>
<td>Mean: 21.9</td>
<td>Mean: 3.0</td>
<td>While total RF is almost unaffected after surgery, a WIT &gt; 25 min leads to a significant decrease in effective renal plasma flow on the operated side. WIT as a continuous variable is associated with greater loss of RF. ROC analysis identifies 25 min as a soft WIT cut off. Loss of RF occurs within 3 mo and remains stable until 12 mo after LPN. Intraperitone, visually estimated preserved parenchyma volume, radiologic tumor size, and procedure type significantly correlate with postoperative unilateral RF at univariable analysis. No factor is an independent predictor at multivariable analysis.</td>
<td>4</td>
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<tr>
<td>Chan et al [41]</td>
<td>65</td>
<td>OPN (n = 35) LPN (n = 30)</td>
<td>To retrospectively evaluate predictors of postoperative unilateral RF by using renal scans (preoperative; 1 mo postoperative).</td>
<td>OPN: 29.8 ± 9.9</td>
<td>OPN: 3.8 ± 1.9</td>
<td>While total RF is almost unaffected after surgery, a WIT &gt; 25 min leads to a significant decrease in effective renal plasma flow on the operated side. WIT as a continuous variable is associated with greater loss of RF. ROC analysis identifies 25 min as a soft WIT cut off. Loss of RF occurs within 3 mo and remains stable until 12 mo after LPN. Intraperitone, visually estimated preserved parenchyma volume, radiologic tumor size, and procedure type significantly correlate with postoperative unilateral RF at univariable analysis. No factor is an independent predictor at multivariable analysis.</td>
<td>4</td>
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<tr>
<td>Song et al [42]</td>
<td>117</td>
<td>OPN (n = 52) LPN (n = 65)</td>
<td>To investigate factors determining RF decrease. (preoperative; 6 mo postoperative).</td>
<td>OPN: 20.5 (range: 8–35)</td>
<td>OPN: 3.72 (range: 0.9–11)</td>
<td>Renal volume reduction, tumor location, and patient age are independent predictors of postoperative RF at multivariable analysis.</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Popigia et al [44]</td>
<td>54</td>
<td>LPN</td>
<td>To evaluate the long-term effects of WI on RF by using renal scans (preoperative; 3 and 6 mo postoperative; yearly).</td>
<td>Mean: 27.98 ± 11.12</td>
<td>Mean: 3.69 ± 1.39</td>
<td>Split RF of the operated kidney decreases significantly at 3 mo from surgery and subsequently remains stable during follow-up up to 4 yr. WIT is the only independent predictor of split RF at 4 yr from surgery.</td>
<td>4</td>
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Tolerance of the Human Kidney to Isolated Controlled Ischemia

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JASN
Journal of the American Society of Nephrology
PRESENT KNOWLEDGE OF ISCHEMIA IN THE HUMAN KIDNEY

- Current teaching suggests that every minute of renal ischemia increases risk of renal functional impairment
  - Data from: animal, renal transplant, retrospective human studies

- Novel biomarkers implicated in Acute Kidney Injury from diverse causes

- The role of biomarkers in the setting of partial nephrectomy is undefined
GOALS

• In the setting of partial nephrectomy

• To determine if duration of ischemia time impacts renal function

• To evaluate the role of novel biomarkers in predicting renal functional changes
  – Functional Biomarkers
  – Structural Biomarkers
  – Electron Microscopy
  – Immunofluorescence
Trial Design

• 40 patients prospectively enrolled
  – February 2009 – October 2010
  – Informed Consent

• Open partial nephrectomy
  – Single surgeon
  – Uninvolved contralateral kidney
  – No pre-existing end stage renal disease
TRIAL DESIGN

Pre-op
- Urine: Cr, NAG, NGAL, KIM-1, IL 18, MALB, LFABP, CYSC
- Blood: Cr, NGAL, CYSC

Surgery
- Electron microscopy
- Light microscopy
- Immuno-fluorescence

Post-op
- Blood: Urine: Cr, NGAL, CYSC
- At 2 and 24 hours

at 2, 6, 24 hours
BIOPSY SCHEMA

Preclamp:
1 - 2 biopsies

Ischemia:
1 biopsy every 10 minutes or 2 biopsies at the end

Reperfusion:
1-2 biopsies at 5 minutes

Electron microscopy
Light microscopy
Immunofluorescence
Unique attributes

• Surgeon blinded to all clinical, biomarker and structural data till end of the study

• Pathologist and Nephrologist blinded to clinical data till end of study

• Biomarkers evaluated at a lab blinded to all other data
Results

• Mean age – 55 years (range 28-84)

• Median tumor size – 4.1 cm (range 2.0 - 8.0)

• Warm ischemia in 27 and cold ischemia in 13 patients

• Mean duration of ischemia
  – Warm - 32.3 minutes (range 15 - 53)
  – Cold - 48.0 minutes (range 30 - 61)

80% (33/40) of patients had ischemia > 30 minutes
BIOMARKERS

FUNCTIONAL

• SERUM
  – Creatinine
  – Cystatin C

STRUCTURAL

• SERUM
  - NGAL Neutrophil Gelatinase Associated Lipocalin

• URINE
  - NGAL
  - NAG N-Acetyl-Beta-D Glucosaminidase
  - L-FABP Liver Fatty Acid Binding Protein
  - KIM-1 Kidney Injury Molecule-1
  - IL-18 Interleukin-18 -- Inflammation
FUNCTIONAL BIOMARKERS

Transient increase in serum Creatinine

No changes in serum Cystatin C

Serum Creatinine

- p<0.0001 at 24 h
- p = 0.15 at 72 h

Serum Cystatin C

- p=0.94 at 24 h

Recovery Time (hours)

- Pre
- 2
- 24
- 48
- 72
- 96

mg/dl

0.0
0.5
1.0
1.5
2.0

0.79
0.84
0.97
1.08

Recovery Time (hours)

- Pre
- 2
- 24

ng/ml

0.0
0.5
1.0
1.5
2.0

0.0
0.5
1.0
1.5
2.0

p=0.17
p=0.64

p<0.0001
p=0.182

p=0.152
p=0.64
FUNCTIONAL BIOMARKERS

NO CORRELATION WITH DURATION OF ISCHEMIA

X-axis = Ischemia time
Y-axis = 24h to baseline ratio
STRUCTURAL BIOMARKERS

NO CORRELATION WITH DURATION OF ISCHEMIA

$X-axis = \text{Ischemia time}, \quad Y-axis = \text{Peak to baseline biomarker ratio}$
How much of an insult does the normal *human* renal parenchyma sustain under clamp induced ischemic conditions?

ELECTRON MICROSCOPY AND ULTRASTRUCTURE
IN ANIMAL MODELS . . .
5 MINUTES ISCHEMIA

15 MINUTES ISCHEMIA

30 MINUTES ISCHEMIA

RABBIT ISCHEMIA IN VIVO

NORMOXIC

15' ISCHEMIA

30' ISCHEMIA

60' ISCHEMIA
## Composite Scale of Injury on EM

> 300 biopsies, > 2000 EMs reviewed by subject matter authority

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absolutely pristine</td>
</tr>
<tr>
<td>1</td>
<td>Minimal BBM discontinuity, apical membrane blebbing without shedding. <strong>Mild mitochondrial swelling limited to DTs.</strong> Mild occasional IC expansion. Occasional pale cells noted.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Moderate mitochondrial swelling in PTs</strong>, moderate to severe swelling of DTs. Mitochondrial condensation. BBM fragmentation, thinning or discontinuities. Occasional lumenal blebs.</td>
</tr>
<tr>
<td>3</td>
<td>BBM thinning, fragmentation. Lumenal bleb casts. <strong>Uniform higher amplitude mitochondrial swelling in PTs and DTs</strong>, but with preservation of cristae and overall architecture. Changes present in any tubule, but not present in all.</td>
</tr>
<tr>
<td>4</td>
<td>Stage 3 changes <strong>seen in every tubule.</strong></td>
</tr>
<tr>
<td>5</td>
<td>Presence of <strong>necrotic cells</strong> with large amplitude MPT type mitochondrial swelling, <strong>plasma membrane disruption</strong>, loss of cytosolic content.</td>
</tr>
</tbody>
</table>
NORMAL PROXIMAL TUBULE

61 MIN OF COLD ISCHEMIA

REPERFUSION AT 5 MIN
GLOMERULAR ULTRASTRUCTURE
EM staging

The degree of insult at the ultrastructural level was relatively **mild and reversible** in all patients.

Pre = Baseline, End = Maximum duration of ischemia, Post = Reperfusion at 5 mins.
EM INJURY SCORE

NO CORRELATION WITH DURATION OF ISCHEMIA

$X-axis = \text{Ischemia time}, \ Y-axis = \text{EM score difference}$
No changes

Integrin

pTyr

31 minutes of warm ischemia

Reperfusion at 5 minutes

MINIMAL changes
IN A PROSPECTIVE TRIAL

CORRELATIVE ANALYSIS

Functional Biomarkers + Structural Biomarkers + Electron Microscopy + Immunofluorescence =

No correlation with the duration of ischemia time

Minimal structural and functional reversible changes
Long-term response to renal ischaemia in the human kidney after partial nephrectomy: results from a prospective clinical trial

George J.S. Kallingal*, Joel M. Weinberg†, Isildinha M. Reis‡, Avinash Nehra*, Manjeri A. Venkatachalam§ and Dipen J. Parekh*

Table 4 Multivariate analysis of long-term change in creatinine (1 year minus pre-op).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Ischaemia duration as continuous variable</th>
<th>Ischaemia duration &lt;30 min vs ≥30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β estimate* (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td>0.573 (0.029, 1.117)</td>
<td>0.040</td>
</tr>
<tr>
<td>Ischaemia duration</td>
<td>1-min increase</td>
<td>0.003 (−0.004, 0.009)</td>
<td>0.452</td>
</tr>
<tr>
<td></td>
<td>&gt;30 vs ≤30 min (reference)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Ischaemia type</td>
<td>Warm vs cold (reference)</td>
<td>−0.163 (−0.321, −0.005)</td>
<td>0.044</td>
</tr>
<tr>
<td>Creatinine 24-h after surgery minus preoperative</td>
<td>1-unit increase</td>
<td>0.130 (−0.132, 0.393)</td>
<td>0.316</td>
</tr>
<tr>
<td>Tumour size (cm)</td>
<td>1-cm increase</td>
<td>0.004 (−0.041, 0.048)</td>
<td>0.869</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme use</td>
<td>Yes vs no (reference)</td>
<td>0.102 (−0.038, 0.242)</td>
<td>0.148</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1-unit increase</td>
<td>−0.008 (−0.016, 0.000)</td>
<td>0.061</td>
</tr>
<tr>
<td>Age (years) at surgery</td>
<td>1-year increase</td>
<td>−0.006 (−0.011, −0.001)</td>
<td>0.023</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>White non-Hispanic vs Hispanic</td>
<td>0.167 (0.036, 0.299)</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>Gender</td>
<td>Male vs female</td>
<td>−0.005 (−0.126, 0.116)</td>
<td>0.929</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes vs no (reference)</td>
<td>0.085 (−0.048, 0.218)</td>
<td>0.200</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Yes vs no (reference)</td>
<td>0.029 (−0.102, 0.160)</td>
<td>0.650</td>
</tr>
</tbody>
</table>

*R^2* estimate: estimated variable coefficient in predicting long-term change in creatinine. *Coefficient of determination: proportion of variation of the outcome explained by the multivariate regression model. Statistically significant P values are in bold.
We do not suggest that renal ischaemia should not be taken seriously. We believe, however, that the current practice of using ischaemia duration threshold as a dichotomous marker and the commonly suggested ‘safe’ ischaemia values of 20 or 30 min and recently, zero ischaemia, are flawed. Most urologists are able to perform renal tumour excision and parenchymal reconstruction in a timely manner using renal hilar clamping.
ACUTE KIDNEY INJURY

RIFLE CLASSIFICATION
(Risk, Injury, Failure, Loss and End-Stage kidney Disease)

AKIN CLASSIFICATION – Stage 1-3

SIGNIFICANCE OF STAGE 1
AKIN AND EARLY STAGES
OF RIFLE IS UNKNOWN

Loef B G et al. JASN 2005;16:195-200
SIGNIFICANT AKI / DIALYSIS IN CONTEMPORARY PN POPULATION

Less than 1%

AKI 20%  DIALYSIS 3%
RENAL ISCHEMIA – TAKE HOME

• Limited ischemia is safe to perform partial nephrectomy

• Overly simplistic and naïve to consider a single value ischemia time cut off to act as a dichotomous marker for renal injury

• Do not compromise the main goal while performing PN - Sound and Safe Oncologic outcomes
TECHNICAL MODIFICATIONS - ISCHEMIA

• No high level data showing unequivocal benefit of cold over warm

• Animal, transplant and retrospective human studies suggest protective effect of hypothermia

• Temperature and techniques remain dependent on institution and surgeon

• Early unclamping, Off-clamp PN, Selective clamping, Zero ischemia etc …

• Not Necessary
Evaluation of functional outcomes after laparoscopic partial nephrectomy using renal scintigraphy: clamped vs clampless technique

Increased blood loss with zero ischemia approach

No difference in renal functional outcomes between clamp and zero ischemia approaches

Porpiglia et al BJUI 2015
ANATOMIC STUDY OF RENAL ARTERIAL VASCULATURE AND ITS POTENTIAL IMPLICATION ON PARTIAL NEPHRECTOMY

Machhi et al, BJUI January 2017
In 80% of patients, one single renal segment was vascularized by 2 or more different branches coming from an artery destined to another segment.
TECHNICAL MODIFICATIONS TO MAXIMIZE PARENCHYMAL PRESERVATION

• Enucleation
  • Blunt dissection along the pseudocapsule without excision of a rim of normal parenchyma
  • Oncological outcomes appear safe

• Non-renorrhaphy technique
  • No cortical suturing to minimize parenchymal damage
  • No evidence of benefit
TAKE HOME MESSAGE

• Pre and post operative preparation important

• Baseline quality and post operative quantity of renal parenchyma critical

• Renal ischemia safer than earlier thought

• Surgical modifications helpful but must be balanced by oncologic efficacy and morbidity
SUGGESTED READING

- Rod et al. Impact of ischemia time on renal function after partial nephrectomy: a systematic review. BJUI, 2016
In his famous essay “The Hedgehog and the Fox,” Isaiah Berlin divided the world into hedgehogs and foxes, based upon an ancient Greek parable: “The fox knows many things, but the hedgehog knows one big thing.”

Jim Collins