WARMING UP TO ISCHEMIA

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WHAT ARE THE GOALS OF A PARTIAL NEPHRECTOMY FOR RCC?

• Oncologic Efficacy

• Preserve Renal Function

• Reduce Perioperative morbidity

• Cosmesis
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
Tolerance of the Human Kidney to Isolated Controlled Ischemia

Dipen J. Parekh,* Joel M. Weinberg,† Barbara Ercole,* Kathleen C. Torkko,‡ William Hilton,* Michael Bennett,§ Prasad Devarajan,§ and Manjeri A. Venkatachalam‖
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: at 2 and 24 hours
  - Urine: Cr, NAG, NGAL, KIM-1, IL 18, MALB, LFABP, CYSC
  - Blood: at 2, 6, 24 hours
BIOPSY SCHEMA

Preclamping: 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

WARM
COLD

Recovery Time (hours)
Pre 2 24 48 72 96

Serum Creatinine

0.79 0.97
0.84 1.08

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

Serum Cystatin C

0.0 0.5 1.0 1.5

p=0.94 at 24h

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

Serum Cystatin C

0.79 0.97
0.84 1.08

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

Serum Creatinine

0.0 0.5 1.0 1.5

p<0.0001
p=0.182

Serum Cystatin C

0.0 0.5 1.0 1.5

p=0.17
p=0.64

p<0.0001
p = 0.182
FUNCTIONAL BIOMARKERS
NO CORRELATION WITH DURATION OF ISCHEMIA

**Serum Creatinine**
- $\beta = 0.003$
- $p = 0.49$

**Serum Cystatin C**
- $\beta = -0.003$
- $p = 0.48$

**eGFR**
- $\beta = -0.004$
- $p = 0.27$

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

NO CORRELATION WITH DURATION OF ISCHEMIA

X-axis = Ischemia time, Y-axis = Peak to baseline biomarker ratio
## 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
The degree of insult at the ultrastructural level was relatively **mild and reversible** in all patients.
EM INJURY SCORE

NO CORRELATION WITH DURATION OF ISCHEMIA

\[ X\text{-axis} = \text{Ischemia time} \ , \ Y\text{-axis} = \text{EM score difference} \]
Integrin

Actin

No changes

pTyr

MINIMAL changes

Baseline

31 minutes of warm ischemia

Reperfusion at 5 minutes
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 vs &gt;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>Ischaemia duration</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>
<tr>
<td>R²</td>
<td></td>
<td>0.554</td>
<td></td>
</tr>
</tbody>
</table>

*β 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.
How reliable is the evidence that limited ischemia is unsafe?
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.56 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 irreversible functional and structural damage occurs.
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>
</tr>
<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>
</tr>
<tr>
<td>180</td>
<td>100</td>
<td>None</td>
</tr>
</tbody>
</table>

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.
• 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 kidney 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......
SIGNIFICANT AKI / DIALYSIS IN CONTEMPORARY PN POPULATION

→ AKI 20% → DIALYSIS 3%

Less than 1%
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
Renal Ischemia and Function After Partial Nephrectomy: A Collaborative Review of the Literature

Alessandro Volpe\textsuperscript{a,*}, Michael L. Blute\textsuperscript{b}, Vincenzo Ficarra\textsuperscript{c}, Inderbir S. Gill\textsuperscript{d}, Alexander Kutikov\textsuperscript{e}, Francesco Porpiglia\textsuperscript{f}, Craig Rogers\textsuperscript{g}, Karim A. Touijer\textsuperscript{h}, Hendrik Van Poppel\textsuperscript{i}, R. Houston Thompson\textsuperscript{j}

After 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.

Eur Urol 2015
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), WI (n = 174), and CI (n = 278)</td>
<td>0 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>
</tr>
<tr>
<td>Thompson et al [34]</td>
<td>362</td>
<td>OPN (n = 319) LPN (n = 43)</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 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 end points.</td>
<td>4</td>
</tr>
<tr>
<td>Lane et al [5]</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: 17-29) CI median: 45 (IQR: 35-60)</td>
<td>WI median: 4 (IQR: 2.8-5.2) CI median: 4 (IQR: 2.9-5.4)</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 (n = 319) LPN (n = 43)</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>WIT, percentage of kidney preserved, and preoperative GFR were independent predictors of ARF, and only the percentage of kidney preserved and preoperative GFR were independent predictors of new-onset stage 4 CKD during follow-up.</td>
<td>4</td>
</tr>
<tr>
<td>Lane et al [15]</td>
<td>199</td>
<td>OPN (n = 169) LPN (n = 30)</td>
<td>To compare RF outcomes of OPN and LPN and assess predictors of postoperative RF</td>
<td>OPN median: 21 (IQR: 17-27) LPN median: 20 (IQR: 19-35)</td>
<td>OPN median: 3.8 (IQR: 2.8-48) LPN median: 2.8 (IQR: 2.5-3.9)</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>
</tr>
</tbody>
</table>

CI = 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.
<table>
<thead>
<tr>
<th>Study</th>
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<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) PN with no ischemia (n = 96)</td>
<td>OPN (n = 411) LPN (n = 47)</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 (range: 4–55)</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>
<td>3</td>
</tr>
<tr>
<td>Kopp et al [49]</td>
<td>Clamped PN (n = 164) Clampless PN (n = 64)</td>
<td>OPN</td>
<td>To analyze factors affecting postoperative RF using both the clampless and clamped warm ischemic technique</td>
<td>Mean: 24.5 0</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 clampless PN. Increasing WIT was an independent predictor of stage 3 CKD after clamped PN.</td>
<td>3</td>
</tr>
<tr>
<td>Smith et al [50] **</td>
<td>Clampless PN (n = 116) Clamped PN (n = 192)</td>
<td>OPN</td>
<td>To determine safety and impact on RF of clampless PN</td>
<td>Mean: 20 0</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 44%; p = 0.027). The rate of complications was similar in the groups. Off-clamp RAPN had a significantly shorter operative time, higher EBL, and smaller decrease in eGFR compared to clamped RAPN.</td>
<td>3</td>
</tr>
<tr>
<td>Kaczmarek et al [52] **</td>
<td>Clampless PN (n = 49) Clamped PN (n = 283)</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 18.5 0</td>
<td>–</td>
<td>5.3 ± 0.2</td>
<td>5.6 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Porpiglia et al [53] *</td>
<td>Clampless PN (n = 44) Clamped PN (n = 42)</td>
<td>LPN</td>
<td>To compare postoperative RF of clampless vs clamped LPN (WIT &lt;25 min) by using renal scintigraphy</td>
<td>Mean: 18 0</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 clampless LPN. Patients with poor preoperative RF had the most benefit with a clampless approach.</td>
<td>3</td>
</tr>
<tr>
<td>Gill et al [54] **</td>
<td>Zero ischemia (n = 58) LPN (n = 43) RAPN (n = 15)</td>
<td></td>
<td>To present the concept and assess the perioperative outcomes of zero ischemia PN</td>
<td>0</td>
<td>Mean: 3.2 (range: 0.9–13)</td>
<td>7 ± 1.9</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Ng et al [55] **</td>
<td>Zero ischemia with VMD (n = 22) Zero ischemia without 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>
<td>3</td>
</tr>
<tr>
<td>Shao et al [58] **</td>
<td>Segmental artery clamping (n = 44) Main artery clamping (n = 31)</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 Mean: 27 ± 5.3</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>
<td>4</td>
</tr>
<tr>
<td>Study</td>
<td>Patients, no.</td>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Popiglia 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>
<td></td>
<td></td>
</tr>
<tr>
<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></td>
<td></td>
<td></td>
</tr>
<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: 4.1</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 the intercurrent medical complications did not have a clinically significant impact.</td>
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<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 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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<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. Once WIT is considered as a continuous variable, it is associated with greater loss of RF. ROC analysis identifies 25 min as a safe WIT cut off. Loss of RF occurs within 3 mo and remains stable until 12 mo after LPN.</td>
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<td>Funahashi et al [40]</td>
<td>32</td>
<td>OPN (n = 20)</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>
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<td>Popiglia 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>
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<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>
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<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>
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<td>Popiglia et al [44]</td>
<td>54</td>
<td>LPN</td>
<td>To evaluate the long-term effects of WIT 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>
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</table>
• “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
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.
TAKE HOME MESSAGES

- **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