Regional Decreases in Renal Oxygenation during Graded Acute Renal Arterial Stenosis: A Case for Renal Ischemia

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SHORT TITLE

Renal oxygenation with renal arterial stenosis
Abstract

BACKGROUND: Ischemic nephropathy describes progressive renal failure, defined by significantly reduced glomerular filtration rate, and may be due to renal artery stenosis (RAS), a narrowing of the renal artery. It is unclear if ischemia is present during RAS since a decrease in renal blood flow (RBF), O₂ delivery, and O₂ consumption occur. The present study tests the hypothesis that despite proportional changes in whole kidney O₂ delivery and consumption, acute progressive RAS leads to decreases in regional renal tissue O₂. METHODS: Unilateral acute RAS was induced in 8 pigs with an extra-vascular cuff. RBF was measured with an ultrasound flow probe. Cortical and medullary tissue oxygen (P₁O₂) of the stenotic kidney was measured continuously with sensors during baseline, 3 sequentially graded decreases in RBF, and recovery. RESULTS: O₂ consumption decreased proportionally to O₂ delivery during the graded stenosis (19±10.8, 48.2±9.1, 58.9±4.7 vs 15.1±5, 35.4±3.5, 57±2.3% respectively) while arterial venous O₂ differences were unchanged. Acute RAS produced a sharp reduction in O₂ efficiency for sodium reabsorption (p<0.01). Cortical P₁O₂ decreases are exceeded by medullary decreases during stenosis (34.8 ± 1.3%). CONCLUSIONS: Decreases in tissue oxygenation, more pronounced in the medulla than the cortex, occur despite proportional reductions in O₂ delivery and consumption. This demonstrates for the first time hypoxia is present in the early stages of RAS, and suggests a role for hypoxia in the pathophysiology of this disease. Furthermore, the notion that arterio venous shunting and increased stoichiometric energy requirements are potential contributors towards ensuing hypoxia with graded and progressive acute RAS cannot be excluded.
Key Words

Renal artery stenosis, ischemia, renal tissue oxygenation, renal blood flow, pig.
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Introduction

The term “ischemic nephropathy” has been used to describe progressive renal failure, defined by a significantly reduced glomerular filtration rate (GFR) or loss of renal parenchyma due to renal artery stenosis, a narrowing of one or more of the renal arteries. Ischemia, however, results from a rate of blood flow that is insufficient to satisfy metabolic demands, thereby leading to tissue hypoxia. There is little evidence to suggest that ischemic nephropathy is accompanied by renal tissue hypoxia. In fact, the kidney has a high blood flow relative to its weight, which results in very small arterial-venous differences in oxygenation, suggesting a large O2 supply and limited O2 consumption. Importantly, Nielsen et al found in patients with significant unilateral renal artery stenosis that O2 consumption decreased with limited blood flow, suggesting that a decrease in O2 supply is not enough to cause ischemic renal disease. Moreover, the reduced O2 supply and demand suggests the term ischemic renal disease is inappropriately applied. In fact, there have been recent suggestions to rename ischemic nephropathy with a more representative term, and also to exclude processes initiated by tissue hypoxia in exploring its pathophysiology.

Moreover, it has been accepted that the high kidney perfusion, which is approximately 20% of cardiac output, results in an O2 delivery (DO2) in excess of metabolic demands. Interestingly, estimates suggest nearly 60% of O2 consumption occurs in the medullary thick
ascending loop of Henle (TAL) where approximately 25% of sodium reabsorption occurs attributable to the 2Cl,Na,K cotransporter. This is in contrast to proximal tubules in the renal cortex where the bulk of sodium is reabsorbed isosmotically. Notably, reductions in renal blood flow (RBF) are known to decrease GFR, and tubular sodium reabsorption, thus decreasing O$_2$ consumption. This effect has fostered the notion that the kidney compensates for reductions in RBF and thus O$_2$ delivery by reducing O$_2$ demand. (2, 3, 8)

The notion that proportional changes in whole kidney O$_2$ delivery and consumption accompany reductions in RBF suggests that renal tissue oxygenation is maintained in equilibrium. Nevertheless, prior work in our lab(7) suggests that renal tissue oxygenation (P$_t$O$_2$) may be impaired during acute renal arterial stenosis. Therefore, the present study was designed to test the hypothesis that despite proportional changes in whole kidney O$_2$ delivery and consumption, acute progressive renal arterial stenosis leads to decreases in regional renal tissue oxygenation. To test this hypothesis and determine if stoichiometric energy requirements are altered, we assessed changes in renal O$_2$ consumption, arterio venous O$_2$ differences, sodium reabsorption and concurrently measured intra-renal tissue oxygenation directly with oxygen electrodes (17, 21, 25) during acute renal arterial stenosis.

Materials and Methods

The experimental protocol was approved by the Mayo Clinic Institutional Animal Care and Use Committee. Eight domestic (Sus Scrofa) pigs (47 ± 2.8 kg) were anesthetized (ketamine 15.7 mg/kg/hr and xylazine 2.33 mg/kg/hr). A catheter was
introduced into the external left jugular vein for infusion of isotonic saline (5 ml/min), 2% inulin, and isoncotic albumin in 0.9% saline (.33% body weight/hr). A catheter was positioned in the left carotid artery for sampling arterial blood oxygen content, and monitoring mean arterial pressure. Body temperature was monitored with a thermoprobe. The animal was kept warm with a warming blanket.

**Surgical preparation**

The right kidney was exposed through a right para-median laparotomy. The kidney was freed of connective tissue, weighed, and placed in a lexan kidney holder (Mayo Clinic, Engineering Services) and held upright by a manipulator stand for the remainder of the experiment. The kidney was surrounded by cotton wool soaked in saline and mineral oil, and kept warm by a saline drip (37 °C). A pneumatic vascular occluder (5-6mm; Harvard Apparatus, Holliston, MA, USA) was placed around the right renal artery, and an ultrasound flow probe (T206 Flowmeter, Transonic) in between the occluder and kidney hilus. Ureters were cannulated bilaterally for urine collection from both kidneys throughout the experiment. A bolus of inulin (60 ml) was followed by a continuous IV infusion of inulin (1 ml/min). Additionally, blood was collected for blood gas measurements from the right renal vein. \( P_iO_2 \) was measured by advancing Clark electrodes (100μm diameter tip, Unisense, Aarhus, Denmark) into the renal cortex and the outer medulla. The tip of the electrode penetrated the right kidney capsule to depths between 0.5-0.8 cm and 1-1.2 cm for cortex and outer medulla, respectively, as verified post-procedure by injection of India ink and dissection. Ventilation rate and tidal volume were adjusted to maintain arterial PO\(_2\), PCO\(_2\) and pH between 90-110mmHg, 35-
50mmHg and 7.3-7.5 respectively. A 45 min rest period preceded the start of urine clearances and experimental maneuvers.

**Experimental protocol**

The experiment comprised 6 sequential maneuvers. The 15 minute duration period of each maneuver allowed for urine, and systemic and right renal vein blood collections. Single kidney inulin clearance was determined from these collections. Systemic arterial and right renal vein samples were collected for blood gas analysis (Instrumentation Laboratory GEM Premier 3000). After a baseline control period, the occluder was initially inflated progressively with an indeflator syringe on the right kidney until RBF started to decrease, and then slightly deflated to restore basal RBF value, which signified the lower limit of RBF autoregulation. A progressive step-wise inflation of the vascular occluder subsequently decreased RBF by 20, 40 and 60% of baseline RBF. The vascular occluder was released for the recovery maneuver.

**Renal hemodynamics and function.**

Plasma and urine inulin concentrations (9) for each clearance period were measured using a standard colorimetric method. GFR was estimated by the clearance of inulin as \( GFR = \frac{U_{inu} \times V}{P_{inu}} \), where \( U_{inu} \) is the urinary concentration of inulin, \( V \) is the urine flow rate (ml/min) and \( P_{inu} \) is the plasma concentration of inulin. Plasma \( P_{Na} \) and urine \( U_{Na} \) sodium concentrations were measured with a flame photometer (IL943, Instrumentation Laboratory, Monza, Italy). The amount of sodium reabsorbed was
calculated as $T_{Na} = P_{Na} \times GFR - U_{Na} \times V$. Percent changes reported reflect the averaged outcome from calculations for each maneuver with respect to baseline.

**Calculation of renal oxygen delivery, consumption and extraction ratios.**

Renal oxygen consumption, $V_{rO_2}$ (ml/min/100 g), was calculated as the product of RBF and the arterial-venous difference in $O_2$ content and normalized for renal weight(7, 8). The arterial oxygen content was calculated by $C_a = (1.31 \times Hb \times S_{aO_2}) + (0.003 \times P_{aO_2})$ and the renal venous content as $C_v = (1.31 \times Hb \times S_{rvO_2}) + (0.003 \times P_{rvO_2})$, where Hb is hemoglobin concentration (mg/dl), $SO_2$ is $O_2$ saturation (%) determined by blood gas analysis in the artery (a) or vein (rv) and $PO_2$ is the arterial (a) or renal vein (rv) oxygen tension (mmHg). Renal oxygen delivery, $DO_2$, was calculated as $DO_2$ (ml/min/100g) = RBF*$C_a$ and similarly normalized for renal weight. Renal oxygen extraction ratio, $O_2ER$, was calculated as $O_2ER$ (%) = $V_{rO_2}$ / $DO_2$ while the $O_2$ efficiency for tubular sodium reabsorption was determined by the ratio of tubular sodium reabsorption (T$_{Na}$) to $V_{rO_2}$.

**Tissue oxygenation.**

The Clark electrodes were connected to A/D converters, OxyMeter (Unisense, Aarhus, Denmark). Digitized data was collected in 1 second intervals for the duration of the experiment with Sensor Trace Basic v1.3 (Unisense, Aarhus, Denmark) and each probe’s data was averaged for the representative maneuver period. The sensors were calibrated in a 21% oxygenated Lactate Ringer solution and an anoxic sodium bisulfide solution at 37°C. The criterion for probe calibration was a successful validation (±2
mmHg) with two samples of arterial and venous blood (20 cc) having different PO$_2$
values (95±2.7 and 44±3.0 mmHg) measured prior to experimental maneuvers.

**Statistical analysis.**

Repeated measures analysis of variance (R-ANOVA) was used to test the
changes due to interventions with post-hoc comparisons to baseline conducted with
Dunnet’s test. Differences between parameters measured on the occluded and
contralateral kidneys (Table 1 and 2) were tested with a paired t-test. Results are
reported as mean ± SEM with statistical significance (p<0.05), unless otherwise noted.

**Results**

**Renal Hemodynamics and Function.**

Decrements in RBF (Fig 1A) by 40 and 60% of control levels (235 ± 25.9 ml/min)
were accompanied by proportional and significant falls in GFR(Fig 1B) as well as
sodium reabsorption(Fig 1C), while decreases to autoregulation and by 20% reduced
RBF did not produce significant changes from baseline. (Table 1) GFR and T$_{Na}$ of the
acutely stenotic kidney returned to baseline values during recovery. Mean arterial
pressure (85.3 ± 0.6 mmHg), arterial and venous oxygen tension remained steady
throughout the procedure (Table 1). No significant change from baseline in GFR, or T$_{Na}$
in the contralateral kidney was observed during these maneuvers. (Table 2)

**Renal O$_2$ delivery, extraction ratio (O$_2$ER) and transport efficiency.**
Renal O₂ delivery was not altered during the decrease of RBF within the range of autoregulation and following a 20% reduction in RBF (Fig 1D), but subsequent decrements in RBF were paralleled by decrements in O₂ delivery and consumption (Fig 1E), suggestive of a balance that should maintain tissue oxygenation. During the stepwise progressive stenosis (by 40 and 60 of RBF), total renal O₂ consumption decreased significantly from the control period in the stenotic kidney (Table 1) (-48.2±9.1 and -58.9±4.7%, respectively, p<0.01) matched by comparable decreases in GFR (-63.6 ± 14.6, and -88.5 ± 4.8%, p<0.01, Fig 1B) and T_Na (-65.9 ± 13.9 and -89.5 ± 4.3%, p<0.01, Fig 1C), the major determinant of O₂ consumption, and recovered to control levels during recovery. The arterio-venous oxygen differences (2.7 ± 0.3 mL O₂/min) and O₂ER (18.7 ± 1.9%) did not change from baseline (Table 1) with reductions in RBF. However, less sodium was reabsorbed per mol of O₂ with reduced RBF as evidenced by the reduced O₂ efficiency for sodium reabsorption. (Table 1) The O₂ efficiency for sodium reabsorption returned to baseline values with recovery.

**Effects of progressive reduced RBF on tissue oxygenation.**

A representative experiment is shown in Figure 2 as a time condensed recording of tissue oxygenation. The baseline aggregated PₜO₂ value was higher in the cortex compared to the medulla (48 ± 1.6 vs. 30.8 ± 1.6 mmHg, p<0.001). As shown in Figure 3, reduced RBF below the range of RBF auto-regulation was accompanied by decreases in renal medullary O₂ tension (34.8 ± 1.3%) more amplified than cortical oxygen tension decreases. Importantly, during progressive decreases in RBF, O₂ tensions fell (Fig. 3) despite O₂ delivery and consumption decreases. (Fig. 1D,E)
Discussion

The main new finding from this study is the decrease in directly measured regional renal tissue oxygenation (more pronounced in the medulla than the cortex) during graded acute renal arterial stenosis. The decreased tissue PO2 during acute and progressive renal arterial stenosis supports the notion that tissue hypoxia occurs despite the concurrent fall in whole kidney O2 delivery and consumption. An important observation from this study indicates for the first time that renal ischemia occurs during acute progressive renal arterial stenosis despite conventional measures failing to indicate the presence of ischemia. The decreases in renal tissue oxygenation implicate factors contributing to hypoxia that may alter local tissue O2 delivery and consumption, as opposed to whole kidney alterations.

Interestingly, in a chronic 2 kidney 1 clip rat model of Goldblatt hypertension, Palm et al (20) demonstrated reduced cortical PO2 in the clipped kidney, underscoring the present findings. Similarly, Johannes and colleagues (6) found a decrease in cortical and medullary tissue PO2, in venous PO2 and a widening of the venous/tissue PO2 gap during acute normovolemic hemodilutions. Further, their study showed an aggressively amplified O2 extraction ratio which counterbalanced their conclusion that arterio venous (a-v) O2 shunting was increased. Nevertheless, the present study extends the findings of Palm and conclusions of Johannes by concurrently demonstrating an accelerated decline in medullary PiO2 (with respect to cortex) while in the presence of stable O2 extraction ratios and a-v O2 differences. Furthermore, this study demonstrates decreases in O2 delivery concurrently with O2 consumption.
The observed hypoxic response to acute RBF reductions suggests for the first time that not only is the term ischemia appropriate, but further indicates that renal arterial stenosis involves hypoxia to a greater extent in the medulla compared to the cortex. This is in agreement with clinical observations of medullary vulnerability to abrupt decreases in renal perfusion.(4, 5, 23) Hypoxia occurs despite the lack of an overall O₂ delivery and consumption mismatch thus implying that global measures of renal hemodynamics are insufficient to fully explain regional differences.

While our present findings cannot fully explain the increased hypoxia, several possibilities merit mention. For example, reduced perfusion may selectively increase O₂ consumption by facilitating reabsorption activities in TAL(1). The possibility of redistribution in sodium reabsorption along the medullary TAL warrants further investigation. The reduced efficiency or ratio of T_{Na} to O₂ consumption may suggest basal metabolic consumption has an increased impact on the diminished local supply of O₂. Moreover, the reduced O₂ efficiency for sodium reabsorption may reflect the increased impact of medullary O₂ consumption occurring due to a shifting of reabsorption from paracellular to transcellular pathways, resulting in increased stoichiometric energy requirements. Furthermore, arterio venous shunting(12, 18, 25) may also occur during progressive renal arterial stenosis, and warrants further investigation.

Due to the parallel arrangement of descending and ascending vasa recta, important for the concentrating mechanism, the kidney is subjected to “shifting” or shunting of arterial O₂ to the venous side.(11, 16, 25) Shunting accounts for both the higher O₂ concentration in the renal vein with respect to the superficial cortex and for
the very low $O_2$ concentration in the renal papilla. (3, 25) The contribution of this mechanism to renal hypoxia however, is unclear. Nevertheless, the notion that a-v shunting occurs during progressive renal arterial stenosis, and the added possibility that stoichiometric energy requirements are increased, due to shifting reabsorption from paracellular to transcellular pathways, cannot be excluded as potential contributors to tissue hypoxia.

The present study demonstrates that despite the lack of an $O_2$ delivery and consumption mismatch, regional ischemia may exist during acute renal arterial stenosis, and suggests that hypoxia may play a role in pathophysiology. While the present study demonstrates variations in intra-renal $P_{tO_2}$ associated with healthy kidneys in an acute situation, future studies will need to explore changes in tissue $PO_2$ within chronic disease. The Clark type $O_2$ electrodes measure $O_2$ through the consumption of $O_2$ at the tip of the electrode (11, 19, 20, 25) and are limited by the need for penetration of the kidney capsule, but are considered as a reference standard for assessment of tissue oxygenation. (10) Recent advances in polymer biomaterials may offer a promising coating that may improve future sensor biocompatibility. (10) Our observations in swine have particular clinical relevance because the pig kidney is anatomically and physiologically comparable to the human kidney (13, 14). Future studies should also examine renal tissue $PO_2$ in conjunction with chronic renal arterial stenosis.

**Perspectives and Significance**

Importantly, in this study we measured the concomitant changes in both cortical and medullary tissue $O_2$ and demonstrated that medullary losses in tissue oxygenation exceed those of the cortex during RBF, $O_2$ delivery and consumption reductions.
Overall, our findings underscore the complex relationship between many hemodynamic variables, and highlights that global renal supply and demand may not be representative of local conditions and may mask regional disparity. Although conventional methods may downplay the existence of renal ischemia in acute renal arterial stenosis, the present study provides convincing evidence that hypoxia may be present in the early stages of acute renal arterial stenosis. Moreover, the evidence for renal ischemia during acute progressive renal arterial stenosis may provide important support for the role that hypoxia may play in the pathophysiology of this disease. The current findings may also implicate factors such as redistribution of sodium reabsorption along the medullary TAL, the shifting of reabsorption from paracellular to transcellular pathways possibly increasing stoichiometric energy requirements, increased impact of basal metabolic demands upon a diminished supply, and enhanced renal arteriovenous oxygen shunting as potential mediators of micro-vascular and glomerular disease that precede direct and detectable effects upon the kidney.

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Footnotes
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Table 1. Whole kidney hemodynamic response of the acutely stenotic kidney to progressive acute renal arterial stenosis at baseline (BL), autoregulation (AR), 20% (20), 40% (40), and 60% (60) decrease in RBF, and recovery (REC).

<table>
<thead>
<tr>
<th></th>
<th>GFR</th>
<th>TNa</th>
<th>DO₂</th>
<th>VrO₂</th>
<th>TNa / VrO₂</th>
<th>A-V O₂</th>
<th>P VO₂</th>
<th>O₂ER</th>
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<tbody>
<tr>
<td></td>
<td>mL / min</td>
<td>mol / min</td>
<td>mL / min /100 g</td>
<td>mL O₂ / min /100 g tissue</td>
<td>mol Na / mL</td>
<td>mL O₂ / min /100 g tissue</td>
<td>mmHg</td>
<td>%</td>
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<td>BL</td>
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<td>32.1±5.7</td>
<td>6.1±.5</td>
<td>.92 ± .1</td>
<td>2.67 ± .3</td>
<td>48.8 ± 1.9</td>
<td>18.7 ± 1.9</td>
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<td>AR</td>
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<td>4.3 ± 0.5</td>
<td>31.2±4.7</td>
<td>5.8±.5</td>
<td>.94 ± .1</td>
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<td>25.6±4</td>
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<td>40</td>
<td>15.2±7.6</td>
<td>1.9 ± 0.8</td>
<td>19.7±3.3</td>
<td>2.7±.3</td>
<td>.58 ± .2</td>
<td>2.14 ± .2</td>
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<td>60</td>
<td>4.9±2.6</td>
<td>0.58 ± 0.3</td>
<td>13±1.8</td>
<td>2.3±.3</td>
<td>.26 ± .1</td>
<td>2.18 ± .14</td>
<td>47.8 ± 1.5</td>
<td>15.5 ± 1.0</td>
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<td>REC</td>
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<td>28.3±5.5</td>
<td>5.4±3.</td>
<td>.65 ± .2</td>
<td>3.13 ± .26</td>
<td>49 ± 1.9</td>
<td>21.7 ± 2.1</td>
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</tbody>
</table>

* p<0.01 compared to baseline.

GFR: glomerular filtration rate, TNa: tubular sodium reabsorption, DO₂: oxygen delivery percent change, VrO₂: renal oxygen consumption measured from arterial venous differences, TNa / VrO₂: O₂ efficiency for sodium reabsorption, A-VO₂: Arterio-venous oxygen differences, P VO₂: renal vein O₂ tension, O₂ER: oxygen extraction ratio in the stenotic kidney.
Table 2. Renal Hemodynamic responses of the contralateral kidney to progressive acute renal arterial stenosis.

<table>
<thead>
<tr>
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<th>$T_{Na}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mL/min</td>
</tr>
<tr>
<td>BL</td>
<td>39.1 ± 5.6</td>
</tr>
<tr>
<td>AR</td>
<td>40.2 ± 5.3</td>
</tr>
<tr>
<td>20</td>
<td>43.5 ± 6.1</td>
</tr>
<tr>
<td>40</td>
<td>53.3 ± 8.2</td>
</tr>
<tr>
<td>60</td>
<td>40.1 ± 5.6</td>
</tr>
<tr>
<td>REC</td>
<td>48 ± 7.6</td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate, $T_{Na}$: tubular sodium reabsorption
Titles and legend to figures and tables

Figure 1. Mean ± SEM % change from control in (A) RBF (B) glomerular filtration rate, and (C) tubular sodium reabsorption, (D) renal oxygen delivery and (E) renal oxygen consumption. * p<0.05 with respect to the control period for a decrease in RBF to autoregulation (0 (AR)), by 20% (20), 40% (40), 60% (60), and recovery (0 (Rec))

Figure 2. Renal cortex and medulla tissue oxygenation measured during an experiment for control period (0(BL)), decrease in RBF to autoregulation ((0 (AR)), by 20% (20), 40% (40), 60% (60), and recovery (0 (Rec))

Figure 3. Percent change in tissue O₂ from BL for the cortex and medulla during acute stenosis for decrease in RBF to autoregulation ((0 (AR)), by 20% (20), 40% (40), 60% (60), and recovery (0 (Rec)). * p<0.05 with respect to BL, † p<0.05 with respect to the medulla for the same period.
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