Long-term measurement of renal cortical and medullary tissue oxygenation and perfusion in unanesthetized sheep

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Calzavacca P, Evans RG, Bailey M, Lankadeva YR, Bellomo R, May CN. Long-term measurement of renal cortical and medullary tissue oxygenation and perfusion in unanesthetized sheep. Am J Physiol Regul Integr Comp Physiol 308: R832–R839, 2015. First published March 11, 2015; doi:10.1152/ajpregu.00515.2014.—The role of renal cortical and medullary hypoxia in the development of acute kidney injury is controversial, partly due to a lack of techniques for the long-term measurement of intrarenal oxygenation and perfusion in conscious animals. We have, therefore, developed a methodology to chronically implant combination probes to chronically measure renal cortical and medullary tissue perfusion and oxygen tension (tPO2) in conscious sheep and evaluated their responsiveness and reliability. A transit-time flow probe and a vascular occluder were surgically implanted on the left renal artery. At the same operation, dual fiber-optic probes, comprising a fluorescence optode to measure tPO2 and a laser-Doppler probe to assess tissue perfusion, were inserted into the renal cortex and medulla. In recovered conscious sheep (n = 8) breathing room air, mean 24-h cortical and medullary tPO2 were similar (31.4 ± 0.6 and 29.7 ± 0.7 mmHg, respectively). In the renal cortex and medulla, a 20% reduction in renal blood flow (RBF) decreased perfusion (14.6 ± 8.6 and 41.2 ± 8.5%, respectively) and oxygenation (48.1 ± 8.5 and 72.4 ± 8.5%, respectively), with greater decreases during a 50% reduction in RBF. At autopsy, minimal fibrosis was observed around the probes. In summary, we have developed a technique to chronically implant fiber-optic probes in the renal cortex and medulla for recording tissue perfusion and oxygenation over many days. In normal resting conscious sheep, cortical and medullary tPO2 were similar. The responses to and recovery from renal artery occlusion, together with the consistent measurements over a 24-h period, demonstrate the responsiveness and stability of the probes.

renal blood flow; kidney oxygenation; renal artery occlusion; perfusion; tissue oxygen tension.

THE ETIOLOGY OF RENAL FAILURE is highly dependent on the setting in which it occurs. Nevertheless, considerable interest has focused on the potential for renal tissue hypoxia to provide a common pathway in multiple forms of acute and chronic kidney disease (18). Oxygen supply to the kidney via the renal artery far exceeds the kidney’s metabolic requirements, yet the renal medulla, in particular, appears susceptible to the development of hypoxia (8).

Many studies in which medullary tissue PO2 (tPO2) has been measured by polarographic electrodes in experimental animals and humans, breathing air or gas mixtures enriched in oxygen, have provided values of 10–20 mmHg (4, 8, 9, 11, 25), close to the critical tPO2 for isolated tubular cells (5 to 15 mmHg) (2, 3, 13, 14). These observations have led to the concept that the medulla normally operates on the brink of hypoxia and so is highly susceptible to factors that might reduce oxygen delivery or increase oxygen demand (8). However, to our knowledge, all available measurements of medullary tPO2 obtained in experimental animals and man have been obtained in the presence of the potentially confounding effects of anesthesia (1, 4, 6, 7, 16). Critically, anesthesia has been shown to be associated with a reduced renal blood flow (RBF) in rabbits and humans (5, 23), which leads to reduced renal oxygen delivery. Furthermore, recent studies in anesthetized rats and rabbits, using either polarographic electrodes or fluorescence optodes, have provided values of medullary tPO2 close to those of cortical tPO2 (12, 17, 32). Medullary tPO2 was even found to exceed cortical tPO2 in anesthetized rats that had been subjected to chronic sodium restriction (38).

It is, therefore, evident that there is a critical need for techniques that enable measurement of regional kidney tPO2 under physiological and pathophysiological conditions. A technique for continuous and long-term measurement of kidney tPO2 in unanesthetized animals would be particularly useful, as it would allow investigation of the temporal association of tissue hypoxia and the initiation and progression of acute and chronic kidney disease.

Herein, we describe the development and validation of a technique for the continuous measurement of tPO2, laser-Doppler flux (as an index of local perfusion), and temperature in the renal cortex and medulla of unanesthetized sheep breathing room air, using fiber-optic probes. In addition, a flow probe was implanted around the left renal artery of each sheep for measurement of total RBF, and a catheter was placed in the renal vein to allow collection of renal venous blood and so measurement of renal oxygen consumption. We assessed the variations in RBF and cortical and medullary tPO2 and perfusion over a 24-h period and how these variables responded to graded occlusion of the renal artery. Histology was performed post mortem to determine the changes in the renal parenchyma around the implanted optical fibers.

MATERIALS AND METHODS

Animal Preparation

Experiments were conducted on eight healthy adult (1.5–2 yr old) Merino ewes (34.0 ± 1.4 kg). Sheep were housed in individual metabolic cages, given free access to water and fed oat chaff once...
a day. The experimental procedures were approved by the Animal Ethics Committee of the Florey Institute of Neuroscience under guidelines laid down by the National Health and Medical Research Council of Australia.

Sheep underwent two sterile surgical procedures under general anesthesia, at intervals of at least 2 wk. In the first procedure, a carotid arterial loop was created to facilitate subsequent arterial cannulation. During the second procedure, a 4-mm transit-time flow probe (Transonic Systems, Ithaca, NY) was placed on the left renal artery together with a 4-mm inflatable silicone vascular occluder (IVM; In Vivo Metric, Healdsburg, CA). The left renal vein was isolated and cannulated with a Tygon catheter (Cole-Parmer; Boronia, Australia; ID 1.0 mm, OD 1.5 mm, length 80 cm). Custom-built fiber-optic probes (450 μm outer diameter; CP-004-001 Oxford Optronix, Oxford, UK), with 20 mm of optical fiber extending from the outer sheath, were inserted into the renal cortex and medulla along tracks prepared by previous insertion of a 25-gauge needle (514-μm outer diameter). Each combined probe contained a dual-fiber laser-Doppler probe (for estimation of tissue perfusion by measurement of laser-Doppler flux), a single-fiber fluorescence optode (for measurement of tPO2), and a thermocouple (for measurement of tissue temperature) (22, 26, 31). Before insertion, the outer sheath of each probe was joined with PVC glue to a flexible sheet (2.0 × 1.0 cm), made in-house from PVC glue spread thinly on a single layer of gauze, which was then allowed to dry. Each probe was inserted 20 mm, one at an acute angle (~10°), so that the probe tip was positioned within the cortex (~3 mm below the renal capsule) and one at a ~60° angle, so that the tip was in the medulla (6–10 mm below the renal cortex) (Fig. 1). The flexible sheet on each probe had four triangular segments cut out, so that it fitted flush to the kidney surface before it was secured to the kidney capsule with cyanoacrylate adhesive. The positions of the probe tips were confirmed at post mortem.

Following implantation of the fiber-optic probes, a Tygon catheter (ID 1.0 mm, OD 1.5 mm, length 80 cm; Cole-Palmer, Boronia, Australia) was inserted into the carotid artery for the measurement of arterial pressure and collection of arterial blood. To maintain patency of the catheters, heparinized saline (20 IU/ml) was continuously infused at 3 ml/h. Sheep were treated with intramuscular procaine penicillin (900 mg), Ilum Propen; Troy Laboratories, Smithfield, NSW, Australia or Mavlab, Slacks Creek, QLD, Australia) at the start of surgery and daily for 2 days postoperatively. Postsurgical analgesia was maintained with intramuscular injection of flunixin meglumine (1 mg/kg; Troy Laboratories or Mavlab) at the start of surgery, and then 4 and 24 h after surgery. A 5-day recovery period was allowed before experiments began.

All fiber-optic cables and connecting leads were tied to the wool on the sheep’s back and exited the back of the cage over a freely revolving tube (10-cm diameter), allowing continuous 24-h monitoring. The transit-time flow probe was connected to a flow meter (T206; Transonic Systems, Ithaca, NY) for measurement of RBF. The fiber-optic probes were connected to OxyLite 2000 and OxyFlo monitors (Oxford Optronix, Oxford, UK) for measurement of cortical and medullary tissue perfusion and tPO2, and temperature (°C) at 30-s intervals. Arterial pressure, RBF, cortical and medullary laser-Doppler flux, tPO2, and temperature were digitized using a CED micro-1401 interface and recorded on a computer using Spike 2 software (Cambridge Electronic Design, UK).

**Experimental Protocols**

Effects of transient reductions in renal blood flow. Commencing 5 days after surgery, the responses to two levels of occlusion of the renal artery, and subsequent reperfusion, were assessed (n = 8). The vascular occluder was inflated to reduce RBF by 20% or 50%, as measured by the renal flow probe. These maneuvers were performed in random order, on consecutive days. Data were recorded during a 15-min control period, during a 30-min period of renal artery occlusion, and over 15 min after deflation of the occluder. Simultaneous arterial and renal venous blood samples were obtained for oximetry, during the control period, and during the final minute of renal artery occlusion (ABL System 625; Radiometer Medical, Copenhagen, Denmark). Standard formulas were used to calculate renal oxygen delivery [RBF·arterial oxygen concentration (Pao2)], renal oxygen consumption [RBF·(arterial oxygen concentration − renal venous oxygen concentration)], and renal oxygen extraction ratio [(arterial oxygen concentration − renal venous oxygen concentration)/(arterial oxygen concentration)].

Circadian changes in cortical and medullary tissue PO2 and perfusion and total RBF. Eight conscious sheep were studied between the 7th and the 8th day after surgery. Total RBF and cortical and medullary tissue perfusion and tPO2 were recorded at 30-s intervals for at least 5 min every hour over 24 h.
**Histology**

In all cases, the position of the fiber-optic probe tips was determined. In an additional sheep implanted with fiber-optic probes, the kidneys were removed at 8 days postimplantation. The probes were removed from the kidney and a polyester suture (size 0) was inserted into the probe tract to keep the tract open during fixation. A block of kidney containing the suture was fixed in 10% neutral buffered formalin for 24 h, processed into paraffin by standard methods, and 4-μm sections were cut and stained with hematoxylin and eosin and Masson’s trichrome. Sections were examined by light microscopy and assessed for evidence of changes relating to the presence of the probe.

**Statistical Analysis**

Data are presented as means ± SE for normally distributed data, or as geometric mean (95% confidence interval) for variables not normally distributed. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC). All variables were assessed for normality and log-transformed where appropriate. For analysis of the responses to renal artery occlusion, average values during the 15-min period prior to inflation of the cuff were compared with the average of the 30 min during inflation and with the average of the 15-min period after deflation of the cuff. Mixed linear modeling was performed with each sheep treated as a random effect. Main effects were fitted for time and treatment (occlusion) with an interaction between time and treatment used to determine whether treatments behaved differently over time. Comparisons at specific time-points were performed using post hoc t-tests. To account for multiple comparisons, a two-tailed critical value of P ≤ 0.01 was considered to be statistically significant.

**RESULTS**

**Circadian Changes in Cortical and Medullary Tissue PO2 and Perfusion and Total RBF**

In conscious sheep (n = 8), RBF was stable over a 24-h period with a mean level of 220 ± 1 ml/min (Fig. 2). Stability of recordings by the fiber-optic probes was demonstrated by the similar levels of cortical and medullary tPO2 and tissue perfusion at the start and end of the 24-h recording period (Fig. 2). There was little evidence of systematic variations in RBF, tPO2 or laser-Doppler flux over the 24-h period. The mean level of tPO2 in the renal cortex (31.4 ± 0.6 mmHg) was not significantly different from that in the medulla (29.7 ± 0.7 mmHg) (P = 0.07) over the 24-h period. In contrast, over 24 h, the mean level of tissue perfusion in the medulla (787.9 ± 16.6 blood perfusion units (BPU)) was significantly less than that in the cortex (1,106.3 ± 13.2 BPU) (P < 0.001).

**Effects of 20 and 50% Reductions in Renal Blood Flow**

In conscious sheep, occlusion of the renal artery to reduce RBF by 21.4 ± 8.5% (P < 0.001) for 30 min was associated with rapid, significant decreases in cortical (14.6 ± 8.6%) and medullary (41.2 ± 8.5%) perfusion (Fig. 3 and Table 1). The percentage decrease in cortical perfusion was similar to the change in total RBF (P = 0.03), but medullary tissue perfusion decreased proportionally more (P < 0.001). There were significant decreases in cortical and medullary tPO2 (48.1 ± 8.5 and 72.4 ± 8.5%, respectively, both P < 0.001 vs. baseline), which were proportionately greater than the corresponding decreases in perfusion (P < 0.001) (Fig. 3 and Table 1).

Renal artery occlusion that reduced RBF by 48.6 ± 7.2% for 30 min caused significant decreases in both cortical (30.1 ± 7.1%) and medullary (52.1 ± 7.1%) perfusion. The percentage decrease in cortical perfusion was less than the change in total RBF (P < 0.001), but the change in medullary tissue perfusion was similar (P = 0.16). Cortical and medullary tissue oxygenation decreased by 80.7 ± 7.0 and 87.3 ± 7.0% (Fig. 3); both of these decreases were greater than the corresponding reduction in RBF (both P < 0.001). Following release of the renal artery occluder, RBF and renal perfusion and oxygenation in both zones rapidly returned toward control levels. Renal artery occlusion induced increases in mean arterial pressure (MAP) (Table 1), but there were no significant changes in heart rate (HR) with either level of occlusion. PaO2 averaged 90 ± 4 mmHg under control conditions and was not significantly altered by either level of renal artery occlusion.

A patent renal vein catheter was available in four animals. Renal oxygen delivery, consumption, and extraction ratio were determined at baseline and at the end of the 30-min partial occlusion of the renal artery. The 20% decrease in RBF reduced renal oxygen delivery by 28 ± 2% and did not significantly change renal oxygen consumption (−29 ± 9%) or renal oxygen...
extraction ratio (1 ± 9%) (Fig. 4). The 50% occlusion maneuver tended to decrease renal oxygen delivery (−49 ± 3%) and renal oxygen consumption (−35 ± 5%), while increasing renal oxygen extraction ratio (+28 ± 8%) (Fig. 4).

**Histological Findings**

At the end of the experiments, the kidneys were removed, and it was confirmed that the tips of the cortical probes were located within the renal cortex, 2–3 mm from the kidney surface, and the medullary probe tips were located 6–10 mm below the renal cortex, ranging from the inner to outer medulla. On one probe, the optic fiber had pulled back in the sheath and gave tPO2 readings of 0; data from this probe were excluded from the analysis. In all cases, the flexible sheet attached to each probe sheath was well attached to the renal capsule. There was no visible hematoma around any of the probe tips. Around the optic fiber, there was minimal observable damage and little fibrosis in either the cortex or the medulla (Fig. 5).

**Table 1. Changes in hemodynamic and renal variables during 20 and 50% reductions in renal blood flow for 30 min in conscious sheep**

<table>
<thead>
<tr>
<th>RBF, ml/min</th>
<th>Cortical perfusion, BPU</th>
<th>Cortical P&lt;sub,o2&lt;/sub&gt;, mmHg</th>
<th>Medullary perfusion, BPU</th>
<th>Medullary P&lt;sub,o2&lt;/sub&gt;, mmHg</th>
<th>MAP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% ↓ RBF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>225 ± 12</td>
<td>1344 ± 346</td>
<td>30.8 ± 4.1</td>
<td>717 ± 82</td>
<td>34.6 ± 5.5</td>
</tr>
<tr>
<td>Oclusion</td>
<td>176 ± 12*</td>
<td>1147 ± 344*</td>
<td>16.0 ± 4*</td>
<td>422 ± 80*</td>
<td>9.5 ± 5.4*</td>
</tr>
<tr>
<td>Recovery</td>
<td>197 ± 12</td>
<td>1202 ± 346</td>
<td>30.3 ± 4</td>
<td>683 ± 81</td>
<td>27.9 ± 5.5</td>
</tr>
<tr>
<td>50% ↓ RBF</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>231 ± 11</td>
<td>1002 ± 151</td>
<td>30.2 ± 3.5</td>
<td>762 ± 49</td>
<td>30.8 ± 3.2</td>
</tr>
<tr>
<td>Oclusion</td>
<td>119 ± 12*</td>
<td>700 ± 150*</td>
<td>5.8 ± 3.4*</td>
<td>364 ± 46*</td>
<td>3.9 ± 3.1*</td>
</tr>
<tr>
<td>Recovery</td>
<td>200 ± 11</td>
<td>937 ± 151</td>
<td>27 ± 3.5</td>
<td>525 ± 49*</td>
<td>25.9 ± 3.2*</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE; n = 8. *Significant difference (P ≤ 0.01) for time comparison with baseline, mixed linear modeling with post-hoc pairwise t-test comparison. RBF, renal blood flow; MAP, mean arterial pressure; BPU, blood perfusion units.
in anesthetized dogs, rats, and humans breathing room air or gas mixtures enriched in oxygen. These studies have, for the most part, shown a gradient in tPO2 from levels of 30–100 mmHg in the cortex to levels of 10–50 mmHg in the outer medulla, depending on the concentration of oxygen in the inspired air (1, 4, 27, 29). It is likely that one of the main factors accounting for this difference in medullary tPO2 between our current study and many of the previous studies reported in the literature is the confounding effects of anesthesia. Indeed, RBF is reduced under anesthesia in rabbits and humans (5, 23), and in sheep, we find that isoflurane anesthesia reduces RBF by 30–50% (10). Anesthesia might also be expected to enhance the workload of the loop of Henle, through activation of renal sympathetic nerve activity and the renin-angiotensin system (34, 36, 37, 40). Together, these factors may account for the low medullary tPO2 measured in some studies. On the other hand, medullary tPO2 measured by fluorescence optode has been found to be similar to cortical tPO2 in rabbits anesthetized with pentobarbital sodium (15, 17), in which tubular sodium reabsorption is markedly inhibited (21, 32). Medullary tPO2 measured by polarographic electrode has even been found to exceed cortical tPO2 in anesthetized rats subjected to chronic salt restriction (38). Thus, medullary tPO2 appears to be highly dependent upon the prevailing experimental conditions. Furthermore, taken together, with previous findings in anesthetized animals, our current observations suggest that the steepness of the cortico-medullary gradient in tPO2, and the relative degree of hypoxia in the renal medulla, may be greater in anesthetized than in conscious animals. This proposition merits testing through direct comparisons of medullary tPO2 between conscious and anesthetized animals. Our new technique makes this possible.

Our current findings also appear at odds with observations of a cortico-medullary gradient of blood oxygenation in anesthetized humans determined by blood oxygen level-dependent magnetic resonance imaging (BOLD MRI) (35). However, the BOLD MRI signal is likely dominated by the inner medulla, yet our current measurements were made in the outer as well as inner medulla. Furthermore, BOLD MRI provides a measure of blood oxygenation rather than tissue oxygenation. Because of the phenomenon of counter-current oxygen shunting in the renal cortex and medulla, tissue oxygenation, and blood oxygenation may be partially uncoupled in the kidney (19). Nevertheless, there is a clear impetus for more detailed studies of the cortico-medullary gradients in oxygenation in conscious animals and humans.

Renal artery occlusion, that decreased RBF by 20 and 50%, caused percentage decreases in cortical perfusion that were similar to those in total RBF. However, there was a proportionally greater decrease in medullary perfusion. These observations indicate a relative deficit in the autoregulatory capacity of the medullary circulation relative to the cortical circulation in conscious sheep. The issue of the relative autoregulatory capacities of the cortical and medullary circulations remains hugely controversial. We have reviewed this issue in detail previously (20). In brief, depending on the technique used to measure medullary perfusion, the species being studied, and the status of extracellular fluid volume, a whole range of relationships between renal artery pressure and medullary perfusion has been observed. Furthermore, all methods used for measurement of medullary perfusion have limitations. The
critical limitation of laser-Doppler flowmetry, at least in highly perfused organs, such as the kidney, is that it provides a measure of erythrocyte velocity rather than bulk blood flow. In the context of our current findings, additional limitations include the fact that we only assessed responses to two levels of renal artery occlusion and did not measure renal artery pressure. Nevertheless, the apparent deficit in autoregulatory capacity in the medullary circulation, observed under the current experimental conditions, likely also explains why medullary tPO2 was reduced more than cortical tPO2. Importantly, after the occlusion was released, RBF returned toward control levels, and the measured oxygenation and perfusion in both the cortex and medulla returned toward normal. These data, together with the finding of similar measurements at 5 days (Fig. 3) and 8 days (Fig. 2) after implantation and the relatively stable measurements over a 24-h period, provide confidence that the chronically implanted probes provide accurate readings over a number of days and reliably detect changes in regional tissue perfusion and oxygenation.

The reductions in tPO2 induced by partial occlusion of the renal artery were proportionally greater than the reductions in perfusion, both in the cortex and medulla. A possible explanation for this observation is that reductions in local oxygen delivery to cortical and medullary tissue exceeded corresponding reductions in local oxygen consumption. Consistent with this proposition, the more severe stimulus reduced renal oxygen delivery by 49 ± 3%, whereas renal oxygen consumption was reduced by only 35 ± 5% and renal oxygen extraction ratio increased by 28 ± 8%. This proposition is also consistent with previous observations in anesthetized pigs and rabbits, which indicate that the effects of reduced renal perfusion pressure on renal tPO2 depend on the balance between changes in renal oxygen delivery and consumption (15, 41).

There have been previous reports of studies in which renal tPO2 was assessed in conscious animals (24, 30, 39), but in each case, it was only possible to present tPO2 in relative terms rather than as absolute values. Thus, we believe our new method provides an important technical advance over previously available methods. Our findings are in accordance with a recent report in which brain tPO2, measured using fluorescence optodes in chronically instrumented awake rats, remained stable for at least a week after probe-implantation. The authors also found that brain tPO2 strongly correlated with the oxygen content of inspired air (33). These authors also described only a minor inflammatory response in the brain, as we found in the kidney.

Strengths and Limitations

We have demonstrated that chronically implanted fiber-optic probes provide stable readings and detect temporal changes in both tissue perfusion and tPO2 in the renal cortex and medulla in conscious sheep. Furthermore, tissue damage and scarring were relatively minor. Any fibrosis would be expected to lead to an underestimation of tPO2, so is unlikely to account for the relatively high tPO2 that we observed in the renal medulla in the unanesthetized sheep. A major advantage of the fluorescence optode technique over polarographic electrodes is the ability of the former to capture tPO2 over a larger volume of tissue, thus leading to better “averaging” of tPO2, particularly in the renal cortex where there is considerable spatial heterogeneity of tPO2 (26). We have previously shown, at least after acute implantation in anesthetized rabbits, that the combination probe used here responds to changes in tissue oxygenation and perfusion in a manner indistinguishable from the response of individual fluorescence optodes and laser-Doppler flow probes (31). Thus, the measurement of tPO2 does not confound the measurement of laser-Doppler flux, or vice-versa. However, it is likely that fluorescence optodes systematically underestimate tPO2 compared with Clark electrodes (4, 26). Although chronic implan-
Perspectives and Significance

The pathophysiology of acute renal failure, induced, for example, by sepsis, cardiopulmonary bypass surgery, or administration of nephrotoxins, such as radio-contrast agents, is not well understood. It has been proposed that renal hypoxia, particularly in the medulla, is an important mechanism leading to deterioration of renal function, but techniques for the chronic and simultaneous measurement of regional tissue perfusion and oxygenation in conscious animals have not been available. We have demonstrated that fiber-optic probes implanted in the renal cortex and medulla provide stable and reliable readings in conscious sheep. Using these probes, we found that resting cortical and medullary oxygenation were similar and averaged ~30 mmHg. Assessment of the circadian variation of cortical and medullary tissue perfusion and oxygenation, together with the responses to and recovery from renal artery occlusion, indicate that these chronically implanted probes are suitable for long-term measurement of intrarenal regional tissue perfusion and oxygenation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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