Determinants of renal tissue hypoxia in a rat model of polycystic kidney disease

Connie P. C. Ow,1 Amany Abdelkader,1* Lucinda M. Hilliard,1 Jacqueline K. Phillips,2 and Roger G. Evans1

1Department of Physiology Monash University, Melbourne, Australia; and 2The Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

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Oxgen as a Regulator of Biological Systems

POLYCYSTIC KIDNEY DISEASE (PKD) is characterized by enhanced proliferation of the epithelium (25) resulting in the formation of renal cysts (20), renomegaly (50), and abnormalities of the renal vasculature (3, 52). Renal tissue hypoxia also appears to be characteristic of PKD, having been demonstrated using pimonidazole adduct immunohistochemistry, an indirect method for assessing tissue oxygenation (4, 10). These observations indicate that hypoxia is present throughout the renal parenchyma, but that the epithelium lining the cysts is particularly hypoxic (2, 4, 10). However, we are not aware of any previous studies in which renal tissue oxygen tension (PO2) has been measured directly in PKD. Renal hypoxia might be important in PKD in at least two respects. First, there is evidence that in chronic kidney disease renal tissue hypoxia can activate sensory nerves within the kidney to activate the sympathetic nervous system (18). Second, hypoxia may exacerbate progression of PKD by hypoxia-inducible factor-dependent cystogenesis (6, 41).

In chronic kidney disease, an imbalance between renal oxygen delivery (DO2) and consumption (VO2), the main determinants of tissue oxygenation, can result in kidney tissue hypoxia (15). Renal DO2 may be compromised because of the presence of structural abnormalities in the renal vasculature (52), vasoconstriction due to activation of intrinsic factors such as the intrarenal renin-angiotensin system (26), activation of the sympathetic nervous system (22), and/or anemia (1, 11). Renal VO2 might be expected to be augmented in PKD due to the presence of oxidative stress (27) and/or dislocation of membrane transport proteins (9, 24). However, we are not aware of any previous reports of measurement of renal DO2 or VO2 in PKD.

In this study, we quantified renal tissue PO2 by Clark electrode, considered the “gold-standard” method (13), in a Lewis rat model of autosomal recessive PKD (LPK) (28). We also measured renal DO2 and VO2 to test the hypothesis that renal tissue hypoxia in PKD is driven by impaired renal DO2 and inefficient oxygen utilization. Because of the possible confounding effects of anesthesia on renal function, we also assessed creatinine clearance and other markers of chronic kidney disease in unanesthetized LPK and Lewis control rats. The LPK model was chosen because it is a well-characterized model of cystic kidney diseases that is phenotypically similar to PKD in humans, being accompanied by hypertension, activation of the sympathetic nervous system, and cardiac hypertrophy (22, 38, 43, 46). Cyst development in this model is predictable and phenotypically recapitulates the renal pathology of human autosomal recessive PKD. In LPK rats, cystic renal disease develops from early in the postnatal period, arises from dilated segments of collecting ducts, and progresses to renal failure over a period of approximately 24 wk (45).

METHODS

General

Male LPK rats (Nek8/NPHP9 model) (28) (n = 17, 219 ± 14 g) and age-matched Lewis rats (n = 18, 353 ± 9 g) were obtained from the Animal Resources Center (Perth, Western Australia). They were housed in a room maintained at 23–25°C with a 12-h light/dark cycle. The rats were allowed free access to water and standard laboratory rat chow. All procedures were approved in advance by the Animal Ethics
Committee of the School of Biomedical Sciences, Monash University or that of Macquarie University. Experiments were thus conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Protocol 1: Renal Function and Kidney Oxygenation Under Anesthesia

Surgical preparation and experimental protocol. Rats (n = 12 Lewis and 11 LPK) were anesthetized with sodium thiobutabarbital (125 mg/kg ip; Injection: Sigma Aldrich, NSW, Australia), and a tracheostomy was performed to allow artificial ventilation (model 7025, Ugo Basile, SDR Clinical Technology, NSW, Australia). The left carotid artery was catheterized to facilitate the measurement of arterial pressure and collection of blood samples. The right jugular vein was then catheterized for the infusion of maintenance fluid containing 2% wt/vol bovine serum albumin (BSA; Sigma Aldrich, in 154 mM sodium chloride) and [3H]inulin at a rate of 2 ml/h. The degree of saturation of arterial hemoglobin with oxygen was measured continually via pulse oximetry with a sensor placed on the foot (Mouse Ox, Starr Life Sciences, Oakmont, PA). The bladder was also catheterized for collection of urine from the left kidney throughout the protocol for later calculation of glomerular filtration rate (GFR) by determination of the clearance of [3H]inulin using standard methods (34).

Renal venous Po2 was measured by sampling from a catheter inserted into the left renal vein via the right renal vein. Consequently, the right renal artery and vein were ligated. The left kidney was then placed in a stable cup, and a temperature probe (F/OT, 230°C) was inserted into the left renal vein via the right renal vein. Consequently, total renal blood flow (RBF). Upon completion of the surgical preparation and measurements where measurements were made in 1-mm increments, moving from the cortical surface to the medulla and back into the cortex on the other side of the kidney (Fig. 1; 10 mm for Lewis and 15 mm for LPK rats). Urine produced by the left kidney was collected during the clearance period for later analysis. At the end of the clearance period, arterial and renal venous blood samples were taken as at the beginning of the clearance period. The duration of the clearance period was defined by the time it took to generate the measurements of renal tissue Po2 but varied from 32.5 to 133 min (73.5 ± 6.9 min) and did not differ significantly between the two groups of rats.

Measurements and calculations. Arterial pressure, heart rate (triggered by the arterial pulse pressure), RBF, core body temperature, kidney tissue temperature, and Po2 measured by Clark electrode were digitized as previously described (23). GFR was determined by the clearance of [3H]inulin. Urinary and plasma sodium concentration was analyzed using an electrolyte analyzer (Rapidchem, Siemens Healthcare Diagnostics, Bayswater, VIC, Australia). Blood oximetry was performed using a point-of-care device (iSTAT, CG8+ cartridges; Abbott Laboratories, Abbott Park, IL). Renal DO2 was calculated as the product of arterial oxygen content and RBF. Renal VO2 was calculated as the product of the arteriovenous oxygen concentration difference and RBF. Fractional oxygen extraction was calculated as VO2 expressed as a percentage of DO2.

Protocol 2: Arterial Pressure and Renal Function in Unanesthetized Rats

In six Lewis rats and six LPK rats, tail-cuff systolic blood pressure was measured as the average of three measurements after acclimatization to the procedure (NIBP controller, ADI Instruments, NSW, Australia). At the end of the equilibration period, the clearance period commenced. First, a sample of arterial blood (0.5 ml) was taken from which hematocrit was measured. Plasma was then separated from the cellular component for the measurement of the concentrations of [3H]inulin and sodium. Arterial and renal venous blood (0.1 ml) samples were also taken for oximetry. Tissue Po2 was measured using a Clark electrode (10 μm tip, Unisense, Denmark) attached to a micromanipulator, under the guidance of a microscope. Cortical tissue Po2 of both Lewis and LPK rats was measured first, from randomly chosen sites, 2 mm below the cortical surface. In the LPK rats, tissue Po2 in the fluid-filled cysts was measured 1 mm below the cortical surface, ensuring that the tip of the electrode did not pass through the other side of the cyst wall. The tip of the electrode was then moved to a position above the center of the kidney, and a series of measurements were made in 1-mm increments, moving from the cortical surface to the medulla and back into the cortex on the other side of the kidney.
LPK rats were anemic, relatively hypoglycemic, hyperkalemic, and hypocalcemic compared with Lewis control rats, although arterial blood sodium concentration was similar in the two groups (Table 1). Arterial blood HCO3− was less in LPK rats (−15.8%) and Paco2 tended to be less in LPK rats (−17.8%, P = 0.07) than Lewis control rats (Table 1). However, arterial blood pH was similar in the two groups (Table 1). Neither arterial Po2 nor So2 differed significantly between LPK and Lewis control rats (Table 2). Arterial oxygen content was 54% less in LPK than Lewis control rats (Table 2).

Mean arterial pressure (MAP) in the Lewis and LPK rats varied across the surgical preparations for the experiment. Immediately after anesthesia, but before the abdominal wall was breached, MAP averaged 207 ± 9 mmHg in LPK rats and 129 ± 4 mmHg in Lewis control rats (data not shown). Once the midline incision was made, MAP fell sharply, particularly in the LPK rats. Consequently, during the clearance period when urine was collected and tissue Po2 was measured, MAP did not differ significantly in the LPK rats compared with Lewis rats (Fig. 2). Heart rate did not differ significantly between the groups at any stage of the experiment (Fig. 2).

Renal hemodynamics and function. RBF was less in LPK rats than Lewis control rats. The deficit in RBF was −55.5% when RBF was expressed in absolute terms, −34.0% when RBF was corrected for body weight, and −93.5% when RBF was corrected for kidney weight (Fig. 2). All measured indices of renal function were significantly less in LPK rats than Lewis control rats, including urine flow (−72.2%), sodium excretion (−70.7%), and GFR (−99.0%) (Fig. 3).

Renal tissue oxygenation. Tissue Po2 in the outer cortical parenchyma of Lewis and LPK rats, as well as within the superficial cysts of LPK rats, was distributed in a unimodal fashion (Fig. 4). The average Po2 of the superficial renal parenchyma of LPK rats was 60.3% less than that of Lewis control rats (Fig. 5). Po2 within the superficial cysts of LPK rats was 79.1% greater than that within the parenchyma but was still significantly lower than that of the superficial parenchyma of the Lewis control rats (Fig. 5). Regardless of the depth below the cortical surface, or the distance from the cortico-medullary junction, renal tissue Po2 of LPK rats was consistently lower than that of Lewis control rats (Fig. 5).

Renal oxygen consumption and delivery. Renal Do2 was 78.5% less in LPK rats than Lewis control rats due both to the deficit in RBF (−55.5%) and blood hemoglobin content (−56.5%). Renal venous Po2 was 30.9% less, and So2 was 19.8% less in LPK rats than Lewis control rats. As a consequence of the greater fractional oxygen extraction in LPK rats

Table 1. Characteristics of anesthetized Lewis rats and Lewis rats with polycystic kidney disease

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lewis</th>
<th>LPK</th>
<th>P</th>
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<tbody>
<tr>
<td>Morphology</td>
<td></td>
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<tr>
<td>Left kidney weight, g</td>
<td>1.4 ± 0.1</td>
<td>9.4 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left KW/BW, g/kg</td>
<td>4.0 ± 0.1</td>
<td>40.0 ± 2.0</td>
<td>&lt; 0.001</td>
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<tr>
<td>Temperature</td>
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<td></td>
</tr>
<tr>
<td>Core temperature, °C</td>
<td>38.1 ± 0.1</td>
<td>37.8 ± 0.1</td>
<td>0.085</td>
</tr>
<tr>
<td>Renal Cortical Temperature, °C</td>
<td>36.2 ± 0.2</td>
<td>31.6 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arterial blood chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>45.9 ± 1.1</td>
<td>23.8 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin, mg/dl</td>
<td>15.0 ± 0.5</td>
<td>6.7 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>13.0 ± 1.1</td>
<td>6.9 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sodium, mmol/l</td>
<td>136.2 ± 1.3</td>
<td>134.9 ± 2.6</td>
<td>0.66</td>
</tr>
<tr>
<td>Potassium, mmol/l</td>
<td>4.2 ± 0.1</td>
<td>5.2 ± 0.2</td>
<td>&lt; 0.001</td>
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<tr>
<td>Ionized calcium, mmol/l</td>
<td>1.22 ± 0.02</td>
<td>1.07 ± 0.04</td>
<td>0.005</td>
</tr>
<tr>
<td>Po2, mmHg</td>
<td>35.2 ± 2.4</td>
<td>28.9 ± 2.2</td>
<td>0.07</td>
</tr>
<tr>
<td>HCO3−, mmol/l</td>
<td>22.7 ± 0.9</td>
<td>19.1 ± 1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.02</td>
<td>7.44 ± 0.03</td>
<td>0.06</td>
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</table>

Values are means ± SE in Lewis rats (n = 12 for morphology, temperature, arterial blood chemistry) and Lewis rats with polycystic kidney disease (LPK) (n = 11 for morphology and temperature; n = 10 for arterial blood chemistry). KW, kidney weight; BW, body weight. P values are outcomes of Student’s unpaired t-test.

Arterial blood chemistry

Left kidney weight, g 1.4
Left KW/BW, g/kg 4.0
Core temperature, °C 38.1
Renal Cortical Temperature, °C 36.2
Arterial blood chemistry

Hematocrit, % 45.9
Hemoglobin, mg/dl 15.0
Glucose, mmol/l 13.0
Sodium, mmol/l 136.2
Potassium, mmol/l 4.2
Ionized calcium, mmol/l 1.22
Pco2, mmHg 35.2
HCO3−, mmol/l 22.7
pH 7.42

Values are outcomes of Student’s unpaired t-test.

Systemic parameters. LPK rats were significantly lighter (32%) and their left kidneys were significantly heavier (55%) than Lewis rats (Table 1). Kidney weight expressed as a fraction of body weight was 10-fold greater in LPK rats than Lewis control rats. Under the conditions of our experiment, renal cortical tissue temperature was 1.9 ± 0.2°C and 6.3 ± 0.4°C less than core body temperature in Lewis and LPK rats, respectively. Body temperature of Lewis rats did not differ significantly to that of LPK rats. However, cortical tissue temperature was significantly less (−12.8%) in LPK rats than Lewis control rats.
than Lewis rats (8.9%), calculated $\dot{V}O_2$ did not differ significantly between the two groups (Fig. 6). However, sodium reabsorption in LPK rats ($1.7 \pm 1.1 \mu mol/min, n = 5$) was 98% less than that of Lewis rats ($88.3 \pm 18.8 \mu mol/min, n = 12$).

**Protocol 2: Arterial Pressure and Renal Function in Unanesthetized rats**

Systolic arterial pressure in freely moving LPK rats was double that of Lewis rats (Table 3). When compared with Lewis rats, LPK rats had 2.5-fold greater urine flow, 4.3-fold greater plasma creatinine concentration, and 6.6-fold greater blood urea nitrogen concentration. They were also frankly albuminuric. Creatinine clearance per gram body weight in LPK rats was 92% less than that of Lewis rats.

**DISCUSSION**

In the present study, we quantified the degree of hypoxia in the kidneys of LPK rats and demonstrated that tissue hypoxia in this model is driven both by a deficit in $DO_2$ and $V_\dot{O}_2$ that is inappropriately high given the level of tubular sodium reabsorption.

Previous investigations of kidney oxygenation in animal models of PKD have provided qualitative evidence of hypoxia within the walls of renal cysts, using immunohistochemical methods (4, 10). Such methods have two major limitations. First, they are unable to quantify the level of hypoxia. Our current observations show the severity of hypoxia in the LPK model, with $P_{O_2}$ within the superficial cortex being an average 60.2% less than that in Lewis rats. Indeed, relative hypoxia is present across the entire corticomedullary axis. The second major limitation of immunohistochemical methods is that they are unable to provide information regarding levels of oxygen within the cysts themselves. Our current findings indicate that the $P_{O_2}$ within the cysts is approximately double that of the cyst wall. This finding might seem surprising, since oxygen that diffuses into the cyst fluid must come from the wall itself. However, corrosion casts of the renal vasculature of humans with autosomal dominant PKD revealed the presence of a dense network of (albeit abnormal) capillaries surrounding the cyst wall (3, 52) despite a decreased total density of blood vessels within the polycystic kidney (54). The presence of these “vascular capsules” may even be an important mechanism facilitating the growth and proliferation of cysts (52). Thus we speculate that the relatively better oxygenation of the cyst fluid compared with the cyst wall may reflect the delivery of oxygen into the cyst fluid from the network of capillaries on the luminal wall of the cyst. The gradient in $P_{O_2}$ between the cyst fluid and the epithelial cells of the cyst wall can thus be explained by the absence of significant oxygen consumption within the fluid of the cyst but the likely avid oxygen consumption of the cyst wall. Application of the basic principles of.

Fig. 2. Renal and systemic hemodynamic parameters in Lewis control rats and Lewis rats with LPK. Columns and error bars represent means ± SE. Total renal blood flow (RBF) measured using a transit-time ultrasound flow probe during the clearance period (A) was factored for body (B) and kidney (C) weight. Mean arterial pressure (MAP, D) and heart rate (HR, E) were also averaged during the clearance period. $P$ values are the outcomes of Student’s unpaired $t$-test.
diffusion would predict a gradient of PO$_2$ from the cyst to the cyst wall, along the lines of our current observation.

Delivery of oxygen to the kidney is a product of total RBF and the quantity of oxygen carried in arterial blood. Previous studies have demonstrated deficits in RBF (17) and anemia in both human PKD (11) and animal models of PKD (38, 47, 56). However, to our knowledge, the current experiments are the first to quantify the relative contributions of these phenomena to reduced renal DO$_2$ in PKD. We found that both RBF (expressed in absolute terms) and blood hemoglobin concentration in the LPK rat were approximately half of their normal levels in the Lewis rat. Thus anemia and renal ischemia make quantitatively similar contributions to the deficit in renal DO$_2$ in this rat model of PKD. Their combined effects result in a total renal DO$_2$ in the kidney of the LPK rat that is only 22% that of the Lewis control rat.

Renal ischemia is also likely to contribute to renal hypoxia in human PKD. We are not aware of any observations of kidney oxygenation in humans with PKD. Thus we assume that hypoxia is present in human PKD from observations in murine models of the disease (current study, see also Refs. 4 and 10). Effective renal plasma flow was found to be $\sim$12% (17) to 37% (29) less in patients with autosomal dominant PKD compared with unaffected individuals and to decrease with

![Graph A](image1.png)

![Graph B](image2.png)

![Graph C](image3.png)

![Graph D](image4.png)

Fig. 3. Renal function factored for body weight in Lewis control rats and Lewis rats with LPK. Columns and error bars represent means ± SE. Glomerular filtration rate (GFR, A), urine flow (U$_{\text{U}}$, B), urinary sodium excretion (U$_{\text{Na, V}}$, C), and filtration fraction (FF, D) were determined over the clearance period. P values are the outcomes of Student’s unpaired $t$-test.

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![Graph B](image2.png)

![Graph C](image3.png)

Fig. 4. Frequency of the measurements made of tissue PO$_2$ (5-mmHg bins) in the superficial parenchyma of Lewis rats with PDK (LPK) (A, 11 rats), within the cysts of LPK rats (B), and in the superficial parenchyma of Lewis rats (C, 12 rats). n = total number of observations.
In addition to the effects of a deficit in total renal DO2, oxygen delivery to tissue may be further compromised in PKD by the presence of vascular abnormalities and fibrosis. Total kidney volume is markedly increased, reflecting the gross enlargement of the kidneys as a result of cysts expansion (16). Vascular architecture is thus altered, such that capillaries and smaller arterioles are flattened and arterial vessels are often tortuous (52). Perhaps more importantly, interstitial fibrotic tissue gradually replaces normal renal tissue as disease progresses (10, 35, 52). The expansion of interstitial fibrotic tissues will increase the distance over which oxygen must diffuse from the vasculature to metabolically active tissues (predominantly tubules), hence contributing to renal tissue hypoxia.

Despite a very marked deficit in GFR (and thus total sodium reabsorption) in the kidneys of LPK rats, renal VO2 was not less than that of Lewis rats. Thus oxygen consumption independent of sodium reabsorption may be greater in LPK than Lewis rats. It might also be that the efficiency of oxygen utilization for sodium reabsorption is reduced in the kidney of progression of the disease (21, 50). Thus ischemia likely contributes to deficient renal oxygen delivery, and thus renal hypoxia, in human PKD. While anemia does develop with the advancement of PKD in humans (8), it is not as severe as this animal model. Thus it seems likely that anemia makes a smaller contribution to renal hypoxia in human PKD that in rodent models of PKD.

Fig. 5. Renal tissue oxygenation of Lewis rats (n = 12) and Lewis rats with LPK (n = 11). Columns and error bars represent means ± SE. A: tissue oxygen tension (Po2) of the superficial parenchyma of Lewis rats and LPK [LPK (P)] rats, and within the cysts of LPK rats [LPK (C)] was measured using a Clark electrode during the clearance period. B: a series of measurements of tissue PO2 were made in 1-mm increments, moving from the cortical surface to the medulla and back into the cortex on the other side of the kidney. C: tissue PO2 is also presented relative to the corticomedullary junction (CMJ). P values are the outcomes of Student’s unpaired t-test.

Fig. 6. Renal oxygen delivery (DO2), oxygen consumption (VO2), and fractional extraction of oxygen (FeO2) of Lewis rats and LPK rats. Columns and error bars represent means ± SE of DO2 (Lewis; n = 12, LPK; n = 10; A), VO2 (Lewis; n = 5, LPK; n = 5; B), and FeO2 (Lewis; n = 5, LPK; n = 5; C). P values are the outcomes of Student’s unpaired t-test.
We must acknowledge a number of limitations to our study. First, the MAP of LPK rats fell during surgical preparations in protocol 1. Hypertension in unanesthetized LPK rats has previously been documented by tail-cuff plethysmography (38), direct measurement from the tail artery (10), and radiotelemetry (19). There is strong evidence for a role of activation of the sympathetic nervous system in the development of hypertension in LPK rats (19). In the current study we confirmed the presence of hypertension in conscious LPK rats by tail-cuff plethysmography. RBF and GFR are tightly autoregulated across relatively wide ranges of arterial pressure (39, 49). However, once arterial pressure falls below the autoregulatory range, both RBF and GFR become dependent on its level. We did not assess renal autoregulation in the current study but can be fairly confident that the marked fall in arterial pressure, observed in LPK rats during preparation for the experiment, led to some degree of underestimation of both RBF (and so renal VO₂) and GFR (and thus the tubular reabsorptive load) with respect to their values in the unanesthetized rat. Consequently, our findings may overestimate the contribution of reduced DO₂, and perhaps underestimate the contribution of inappropriately high VO₂, to renal tissue hypoxia in the LPK model. However, our finding that the deficit in creatinine clearance in unanesthetized LPK rats compared with Lewis rats was comparable to the deficit in [³H]inulin clearance when these animals were under anesthesia gives us some level of confidence in the generalizability of our findings. A second limitation of our study stems from the fact that the animals used in protocol 1 were studied after acute unilateral nephrectomy, which might be expected to alter renal hemodynamic function. Indeed it has been shown that RBF in the remaining kidney increases in the 2 h after unilateral nephrectomy (55). Consequently, unilateral nephrectomy in our current study may have led to increased RBF and thus renal DO₂.

In conclusion, the kidneys of LPK rats are severely hypoxic. There is a deficit in renal DO₂ that is partly due to renal ischemia and partly due to anemia and thus reduced oxygen carrying capacity of arterial blood. But in addition, VO₂ is inappropriately high in the LPK kidney when one considers the minimal level of sodium reabsorption in these rats under the conditions of the current experiment. The specific causes of renal “dysoxia” in PKD merit further investigation.

Perspectives and Significance

PKD commonly progresses to end-stage renal disease, thus represents a significant burden on patients, their families, and health systems (31). Progression of PKD appears to be driven by multiple factors, including signaling pathways driven by cAMP (33) and vascular endothelial growth factor (48). Recent observations in experimental models of PKD have provided evidence for a role of hypoxia-inducible factors in cyst expansion in PKD (5). Consequently, renal tissue hypoxia may represent an important therapeutic target in PKD. Our current work characterized the nature of hypoxia and its causes in a rat model of PKD. Further characterization of the causes of hypoxia, at a molecular level, may lead to new approaches to delay the progression of PKD to end-stage renal disease.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


