

Oxygen and Renal Hemodynamics in the Conscious Rat

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Abstract. Previous studies have suggested a link between renal metabolism and local kidney hemodynamics to prevent potential hypoxic injury of particularly vulnerable nephron segments, such as the outer medullary region. The present study used three different inspiratory oxygen concentrations to modify renal metabolic state in the conscious rat (hypoxia 10% O₂, normoxia 20% O₂, and hyperoxia 100% O₂). Renal blood flow (RBF) was assessed by ultrasound transit time; renal perfusion pressure (RPP) was controlled by a hydroelectric servo-control device. Local RBF was estimated by laser-Doppler flux for the cortical and outer medullary region (2 and 4 mm below renal surface, respectively). Hypoxia led to a generalized significant increase in RBF, whereas hyperoxia-induced changes did not (hypoxia 6.6 ± 0.6 ml/min *versus* normoxia 5.7 ± 0.7 ml/min,

$P < 0.05$). Moreover, regional and total RBF autoregulation was markedly attenuated by hypoxia. Conversely, hyperoxia enhanced RBF autoregulation. Under normoxic and hyperoxic conditions, medullary RBF was very well maintained, even at low RPP (medullary RBF: approximately 70% of control at 50 mmHg). The hypoxic challenge, however, significantly diminished the capacity to maintain medullary blood flow at low RPP (medullary RBF: approximately 30% of control at 50 mmHg, $P < 0.05$). These data suggest that renal metabolism and renal hemodynamics are closely intertwined. In response to acute hypoperfusion, the kidney succeeds in maintaining remarkably high medullary blood flow. This is not accomplished, however, when a concomitant hypoxic challenge is superimposed on RPP reduction.

A very low fraction of delivered O₂ is extracted by the kidney (1). Paradoxically, however, the kidney is extremely susceptible to hypoperfusion, with acute renal failure being one of the most frequent complications of severe hypotension. Renal autoregulation consists of two components: the rapid myogenic response and tubuloglomerular feedback (TGF) (2). One important function of autoregulation is to maintain a balance between the filtered solute load and tubular reabsorption, of which the latter, in part, relies on renal metabolism. Thus, the question arises whether renal metabolism and renal autoregulation are interrelated in some way (3,4). Potential mediators that may link kidney hemodynamics to its metabolism are substances such as adenosine, nitric oxide, ATP, and lactate; furthermore, CO₂ or O₂ may be of importance (2–7).

According to Brezis and Rosen, TGF may reduce filtration when solute concentration at the macula densa is increased due to metabolic requirements (8). A reduction in oxygen supply can thus be compensated for by less filtration. An interesting finding in support of a link between renal metabolism and flow are the rhythmic fluctuations in solute concentration at the macula densa (9). These are mirrored by equivalent waves in partial pressure of oxygen (pO₂) near the glomeruli and tubules.

Although the kidney is an organ with very high perfusion,

not all regions are equally well provided with oxygen. The regional concentration of O₂ in the kidney is determined not only by the metabolic rate, but also heavily depends on the particular vessel arrangement (10,11). Thus, in the superficial layers of the rat kidney (at a depth of 2 mm), pO₂ ranges from 50 to 70 mmHg. Inner layers of the rat kidney, *e.g.*, 4 mm below the capsule, reveal much lower pO₂, amounting to only 20 to 30 mmHg (12,13). Intriguingly, local renal pO₂ is modulated by various stimuli, *e.g.*, cortical and medullary pO₂ are affected independently by changes in renal perfusion pressure (RPP) (13). Moreover, different inspiratory oxygen concentrations may have an impact on regional kidney pO₂ levels. For example, renal medullary pO₂ increases in response to hyperoxic ventilation as indicated by higher urinary pO₂ (14). Although breathing of pure oxygen merely increases oxygen in the dissolved state and does not significantly alter oxygen content, medullary pO₂ nevertheless increases, because of the hairpin arrangement of the vasa recta: The diffusion of oxygen from the descending limb to the ascending limb relies fully on pO₂, and not on O₂ content. Thus, medullary pO₂ increases in response to hyperoxia (15). For the same reason, one may assume that hypoxia reduces renal medullary pO₂ levels. Early experiments, however, have shown that hypoxia-induced renal medullary pO₂ levels do not change as quickly, and not to the same extent, as the renal cortex (12).

If regional flow were not linked to oxygen requirements, local hypoxia, especially at the site of the thick ascending limb, would occur as a consequence of this countercurrent architecture of renal medullary vessels. These vulnerably located cells would, therefore, take damage (16).

The present study was designed to test whether renal blood

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flow (RBF) autoregulation and local RBF are indeed modified by different O_2 concentrations.

Materials and Methods

All experiments were performed on 21 male, adult Wistar rats. Body weight ranged from 300 to 400 g. The rats received a standard rat diet. One day before the measurements, the animals were deprived of food but allowed free access to tap water.

The investigation was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication no. 85-23, revised 1996).

Implantation Surgery

For implantation surgery, general anesthesia was introduced and maintained by chloral hydrate (4% in saline 1 ml/100 g body wt, intraperitoneally). After placing the animals on a thermostat table, the abdominal cavity was exposed by a midventral incision. A catheter connected to a telemetry transmitter (11 PA C40, DSI, St. Paul, MN) was implanted into the infrarenal aorta. The left renal artery and vein were prepared, taking special care not to sever nerve fibers. An ultrasound transit time flow probe (type 1RB; Transonic Systems, Ithaca, NY) was positioned around the left renal artery. Two 500- μ m optical fibers (PF500; Fiberware, Berlin, Germany) were inserted into the renal tissue, one in 2-mm depth (cortical region) and another in 4-mm depth (outer medullary region). They were fixed onto the superior pole of the kidney with a convex plastic holder and a patch. Finally, an inflatable cuff was placed around the suprarenal aorta, below the junction of the superior mesenteric artery. All of the leads and catheters were routed subcutaneously to exit at the nape. After surgery, which was not allowed to exceed 40 min, the rats were housed under constant room temperature and received a single dose of an antibiotic and an analgesic substance (1 ml/kg body wt Tardomyocel; Bayer, Leverkusen, Germany; 1 mg/kg Tramal; Grünenthal, Aachen, Germany).

Measurements

RPP was monitored using the telemetric system; absolute RBF was measured continuously by flow probe. For estimation of regional RBF, the optical fibers were connected via a specifically designed probe and a modified clip to a two-channel laser-Doppler flux monitor (MBF3D; Moore Instruments, United Kingdom). Light leakage along the line was minimized. This system measures tissue perfusion by the number of cells moving and their mean velocity within an area of <1 mm³ beneath the tip of each probe. The laser-Doppler signal (LDS) is independent of the direction of cell movement. The results are expressed in arbitrary perfusion units. Each probe was calibrated using a motility standard. The biologic zero flow, which is required for the resistance calculations, was determined by full inflation of the cuff. Proper location of the optical fibers within the kidney was verified at the end of the experiment by inspecting the location of the fiber tips. Due to the fine ultrastructure of the renal medulla, however, it is not always possible to attribute the 4-mm tip ending to the outer medullary layer only. The laser-Doppler method samples a constant volume of tissue. A reduction of flow is possibly associated with a decrease in tissue volume. The area scanned by the laser, however, remains constant. Thus, more vessels are recruited into the area measured. In addition, prevailing Brownian motion at low perfusion pressure can account for a residual LDS, especially at lower RPP (pooling) (17).

RPP, RBF, and LDS were recorded continuously. After analogue-to-digital conversion, all data were stored online with a sampling rate of 100 Hz (Labtech Notebook 7.3, Woburn, MA).

Experimental Protocols

All experiments commenced in the morning, at least 48 h after surgery. The air-conditioned laboratory was isolated from disturbances. The rats were accustomed to the measuring setup for several days before the experiments. After sufficient training, the rats freely positioned themselves into a restraining tube, which did not allow the rat to rotate around its own axis. The tube was placed into a chamber (20 × 40 × 20 cm), which was used to deliver different gas mixtures (260 L/h air, 260 L/h pure oxygen, and 520 L/h 10% oxygen in nitrogen). The oxygen content of the gas mixture was continuously monitored (Oxytest; Hartmann-Braun, Melsungen, Germany).

The pressure control system adjusted RPP with high precision (2 mmHg). This servo-control device consisted of two components: a syringe pump, which inflated or deflated the cuff with isotonic saline solution, and an additional faster controlling component consisting of a balloon reservoir, whose volume could be rapidly adjusted by compression. In all protocols (see below), the extracorporeal control system changed mean RPP in a ramp-like manner. The clamp was positioned around the aorta, in-between the junction of the superior mesenteric artery and the renal arteries. Thus, perfusion pressure to the hindquarters and to the inferior mesenteric artery is affected by clamping as well. At first, RPP was reduced from 120 mmHg (or the control RPP, when this was <120 mmHg) to 90 mmHg in 400 s. For the pressure range between 90 and 30 mmHg, another 400 s were required. Immediately after reducing pressure, RPP was restored according to the same time regimen (Figure 1).

Six protocols were made (Figure 1, Table 1):

1. Pressure-flow relationship during pressure reduction, under normal air ventilation ($n = 15$)
2. Restoration of RPP during normal air ventilation ($n = 15$)
3. Pressure-flow relationship during pressure reduction, after oxygen content was changed to 100% O_2 ($n = 11$)
4. Restoration of RPP while oxygen content remained at 100% O_2 ($n = 11$)
5. Pressure-flow relationship during pressure reduction, as oxygen content was maintained at 10% ($n = 15$).
6. Restoration of RPP while oxygen content was maintained at 10% ($n = 15$).

The rats were allowed 30 to 40 min to adjust to their environment. After a first control measurement (Figure 1, arrow), the first RPP reduction was performed (protocol 1). Then RPP was restored (protocol 2). A 10-min recovery period was allowed, then a new control measurement was made. Subsequently, the chamber was flushed with pure oxygen and a baseline measurement was obtained after 4 to 5 min (Figure 1, arrows). For protocols 3 and 4, RPP was controlled according to the same regimen as before. Fresh air was brought into the chamber, and after another 10 min, a third control measurement was recorded. Finally, a hypoxic gas mixture was introduced. After obtaining the third baseline value, RPP was again servo-controlled for protocols 5 and 6.

Statistical Analyses

The data were averaged to obtain mean values in steps of 4 mmHg in RPP. Statistical comparisons were made by the Wilcoxon test for paired data. The probability level was set at $2P < 0.05$ to indicate significance, since two comparisons were made. All data are depicted as means \pm SEM.

Results

A representative experiment from one animal is depicted in Figure 1. The gas mixtures in the acrylic chamber were

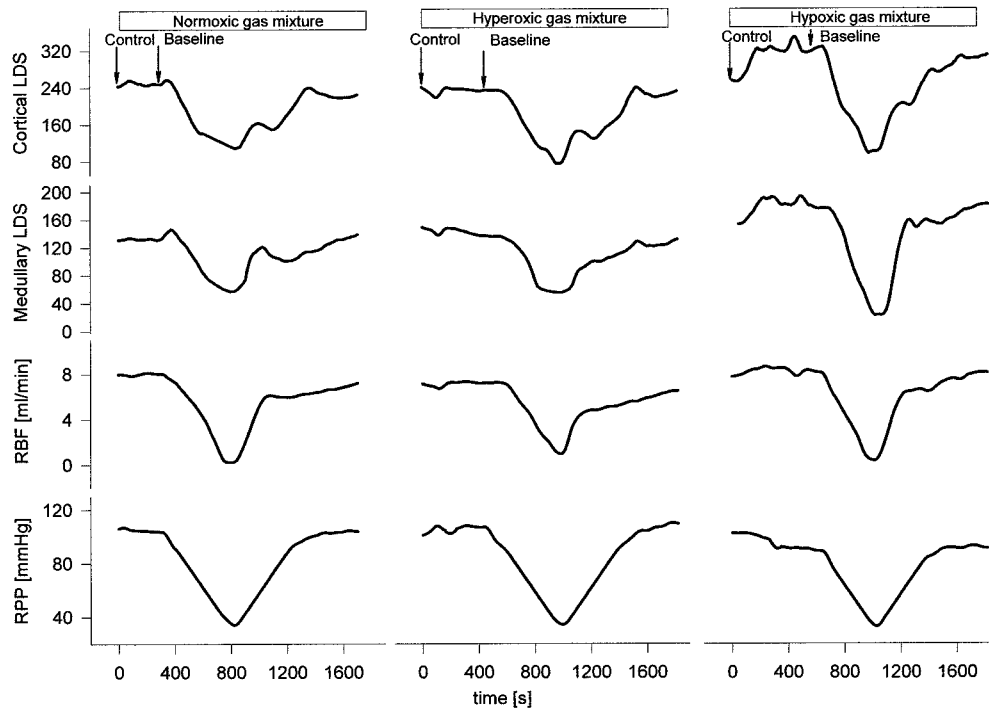


Figure 1. Original recordings of one rat with different O₂ gas mixtures. Traces of renal perfusion pressure (RPP), renal blood flow (RBF), and regional laser-Doppler signal (LDS) are displayed, the latter in arbitrary units (AU). Cortical blood flow is estimated as LDS 2 mm below renal capsule. Outer medullary blood flow estimates are obtained in 4-mm depth. Arrows refer to the time of control measurements, or indicate the baseline values.

Table 1. Baseline values of RPP, RBF, and regional LDS^a

Parameter	Control	Normoxia	Control	Hyperoxia	Control	Hypoxia
RPP (mmHg)	110 ± 4	110 ± 4	109 ± 4	111 ± 4	111 ± 4.4	99 ± 3*
RBF (ml/min)	5.9 ± 0.5	5.8 ± 0.6	5.1 ± 0.6	5.1 ± 0.6	5.7 ± 0.7	6.6 ± 0.6*
Cortical LDS (AU)	301 ± 18	302 ± 18	301 ± 21	301 ± 22	302 ± 19	314 ± 8*
Medullary LDS (AU)	77 ± 11	77 ± 13	76 ± 12	77 ± 11	77 ± 13	109 ± 14*
ΔR RBF (%)		100 ± 2		101 ± 1		70 ± 4*
ΔR CLDS (%)		108 ± 7		104 ± 5		83 ± 8*
ΔR MLDS (%)		100 ± 2		104 ± 4		70 ± 9*

^a Cortical blood flow is estimated as LDS 2 mm below renal capsule. Outer medullary blood flow estimates are obtained in 4-mm depth. RPP, renal perfusion pressure; RBF, renal blood flow; LDS, laser-Doppler signal; ΔR CLDS and ΔR MLDS, percent changes in vascular resistance for the cortex and outer medulla, respectively.

changed as indicated by the bars in this figure. The baseline values of all animals before pressure reduction are specified in Table 1. RBF, cortical LDS, and outer medullary LDS (*i.e.*, LDS in 2 and 4 mm depth) increased during hypoxia by 30, 11, and 41%, respectively ($P < 0.05$). Renal vascular resistance decreased in response to hypoxia. Hyperoxia had no significant effect on these measures.

Figures 2 and 3 depict the pressure-dependent effects of the different gas mixtures on RBF and LDS. The highest pressure values in these figures are not the same as the baseline values in Table 1. This is due to the different individual baseline RPP levels, *i.e.*, not all animals had sufficiently high RPP to be included in the highest pressure value.

As depicted in Figures 2 and 3, autoregulation was markedly blunted by hypoxia. Conversely, hyperoxia increased the autoregulatory pressure range (Figure 2).

Local RBF, as estimated by laser-Doppler flux, is depicted in Figure 3. Outer medullary laser-Doppler flux (4 mm beneath the renal surface) was astonishingly well preserved, even at very low RPP (Figure 3, bottom). For instance, medullary RBF was maintained at 70% of control as RPP was reduced to 50 mmHg. Only in protocol 5, *i.e.*, under hypoxia, did the values take on lower levels. During the hypoxic challenge, medullary blood flow was diminished to approximately 30% of control after adjusting RPP to 50 mmHg ($P < 0.05$).

The outer medullary LDS, however, only provides a quali-

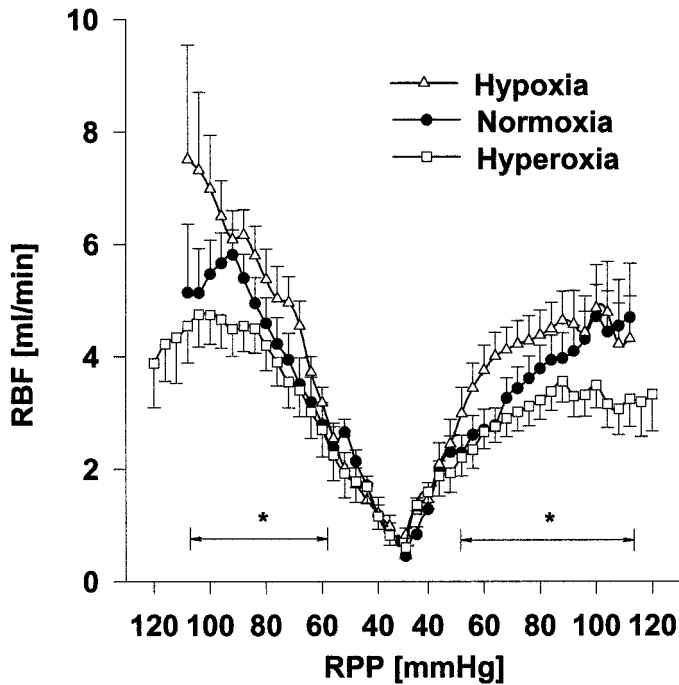


Figure 2. Function relating RBF to RPP for the three different gas mixtures inhaled (Δ , hypoxia [10% O_2]; \bullet , normoxia; \square , hyperoxia [100% O_2]). Autoregulation curves (left half) were obtained by ramp-wise reduction of RPP. Immediately after the RPP decrements, perfusion pressure was gradually restored (right half). * $P < 0.05$, hypoxia versus hyperoxia.

tative measure for blood flow in this region. Erythrocyte pooling and vessel recruitment, as mentioned above (17), can influence the estimate. Furthermore, the erythrocyte concentration may be affected by red blood cell trapping (18), or by plasma skimming.

The cortical LDS, 2 mm below the renal capsule, qualitatively reflects total RBF, *e.g.*, the values for hypoxia are greater than for hyperoxia and the autoregulatory range is reduced. The time course of RBF, however, is not perfectly mirrored by the circumscribed cortical laser-Doppler measurement.

The responses to restoration of RPP were different from the protocols used to derive the pressure-flow relationships (Figures 2 and 3). RBF at normal RPP was reduced considerably. Furthermore, the lower limit of autoregulation was shifted to left (Figures 2 and 3).

Discussion

In the present study, hypoxia decreased RPP and increased total RBF. Local laser-Doppler flux at 2 and 4 mm below the capsule, which were taken as measures for cortical and outer medullary RBF, took on greater values as well (Table 1). RBF autoregulation, as tested by ramp-like RPP decrements, was blunted by hypoxia (Figure 2). Conversely, hyperoxia enhanced RBF autoregulation. Medullary blood flow is very well maintained even at lower RPP (Figure 3). The hypoxic challenge, however, significantly reduced medullary RBF at low RPP, which may reflect the inability to protect vulnerable

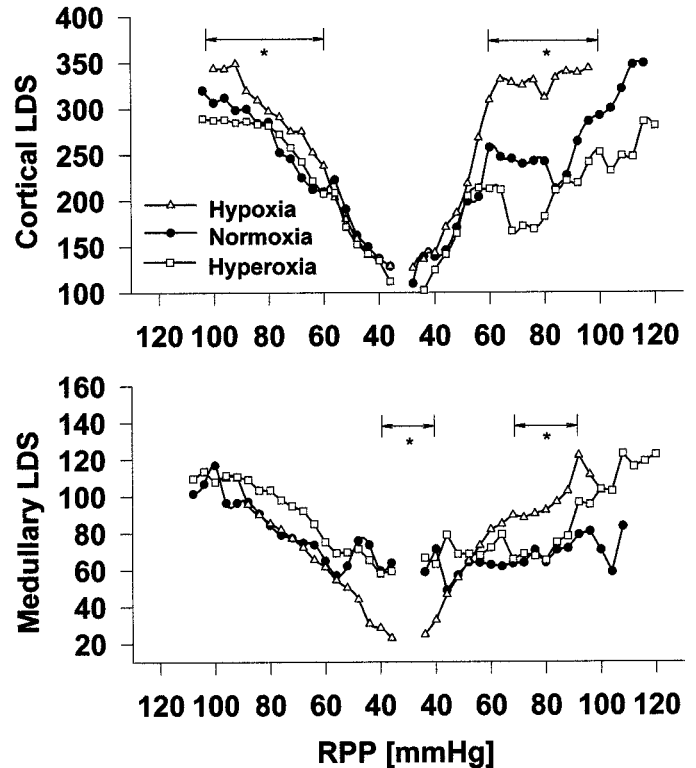


Figure 3. Regional blood flow curves, as estimated by LDS, for the three different gas mixtures inhaled (Δ , hypoxia [10% O_2]; \bullet , normoxia; \square , hyperoxia [100% O_2]). Regional LDS are displayed in arbitrary units (AU). Cortical blood flow is estimated as LDS 2 mm below renal capsule. Outer medullary blood flow estimates are obtained in 4-mm depth. Autoregulation curves (left half) were obtained by ramp-wise reduction of RPP. Immediately after the RPP decrements, perfusion pressure was gradually restored (right half). * $P < 0.05$, hypoxia versus hyperoxia.

nephron segments located in this portion of the kidney. This may have important clinical implications.

Immediately after reaching minimal perfusion pressure in protocols 1, 3, and 5, RPP was slowly restored (right halves of Figures 2 and 3). Protocols 2, 4, and 6, which used incremental ramps, were performed as a model for stabilization after acute hypotension. The effects of restoring RPP on renal hemodynamics are discussed separately from the other protocols, since the reduction of RPP will have affected the neurohumoral and paracrine background of the kidney.

Local Hemodynamics

Outer medullary blood flow does not decrease to the same extent as total RBF or cortical RBF, when RPP is reduced (Figure 3). This may reflect a paradoxical increase in medullary RBF and pO_2 , as described by Brezis *et al.* and Liss *et al.* (10,11). They found a counterintuitive augmentation of medullary RBF, along with an increased medullary pO_2 , by lowering RPP to 70 to 80 mmHg. Corresponding findings have been made for the outlying inner medulla by electron beam computed tomography after reducing RPP to the lower limit of autoregulation (19). The mechanism behind this seemingly

paradoxical increase may be found in vasodilation of the efferent glomerular vessels. The lower limit of GFR autoregulation is higher than that for RBF (20), since efferent vasodilation will reduce filtration and increase RBF. Diminishing efferent vessel resistance has two protective effects. Filtered solute concentration decreases (leading to less oxygen consumption); moreover, local RBF increases and pO_2 is maintained better (10). Indeed, Neylon *et al.* have described such a decrease in GFR combined with an increased renal vascular conductance during hypoxia (21).

Under hypoxic ventilation, these two protective effects cannot take place. The renal vasculature is dilated already at baseline; thus, the capacity to further decrease renal vascular resistance at lower RPP is impaired. Hence, hypoxia significantly decreased outer medullary laser-Doppler flux at low RPP (Figure 3).

In light of the impact of hypoxia on renal medullary circulation, a recently discussed protective mechanism may have particular pathophysiologic significance: nitric oxide bioavailability (22). According to Heyman *et al.*, hypoxia may augment the bioavailability of nitric oxide for physiologic vasodilation (22). This was shown by nitric oxide monitoring (Clark type electrode) after reducing pO_2 from usual levels found in the renal medulla. This mechanism may help alleviate the effects of hypoxia on renal medullary circulation.

The decrease in outer medullary blood flow by combined hypoxia and low RPP may have significant clinical implications, especially in renal injury during various forms of shock. Normally, hypotension is remarkably well compensated for, with only marginal decreases in medullary LDS (Figure 3). Similarly, hypoxia alone did not reduce outer medullary perfusion. This is in line with the clinical observation that usually a combination of several insults or risk factors must take place in order for acute kidney failure to develop (23).

Hyperoxia reduced cortical laser-Doppler flux and diminished total RBF (Figures 2 and 3). This effect, however, is not as pronounced as that found in another study (24), which may rely on the different protocols.

The effect of hyperoxia cannot be ascribed to less adenosine production, since adenosine augments RBF (2). Instead, this observation may rely on the potent vasoconstrictor action of increased pO_2 , as very recently observed by Lombard *et al.* (25). Their experiments suggest that cytochrome P-450 omega-hydroxylase, in some tissues, seems to sense O_2 in the microcirculation.

Pressure-Flow Relationships (Decremental Pressure Ramp)

There were significant effects of hypoxia on total renal autoregulation (Figures 2 and 3): Autoregulation in the face of decreasing RPP was blunted by hypoxia; accordingly, pure oxygen breathing increased the autoregulatory pressure range.

Changing inhaled oxygen concentrations can affect renal hemodynamics via different pathways, *e.g.*, by renal sympathetic nerve activity (RSNA), circulating hormones, or local factors. Several lines of evidence argue against an involvement of RSNA in our protocol. (1) RSNA in rabbits is enhanced by

hypoxia (26,27). However, the current study used rats, which only reveal a meager increase in RSNA by hypocapnic hypoxia (28). (2) Moderate increases in RSNA do not affect baseline RBF (20), whereas more severe increases in RSNA actually reduce RBF (29). Hence, the presented data in Table 1 are opposite to the response one may expect during stimulation of RSNA. Thus, our findings agree well with previous studies by Neylon *et al.* (21,30). A minor role of central nervous effects in mediating the renal response to hypoxia is further underscored by experiments with chemoreceptor stimulation. Perfusion of chemoreceptors with venous blood (31,32) or application of almitrine bismesylate (33), a substance thought to selectively stimulate arterial chemoreceptors, also decreases RBF.

The effects of hypoxia, as seen in Table 1 and Figures 2 and 3, rather seem to rely on other vasoactive factors impinging on myogenic tone and autoregulation. This could be mediated by K_{ATP} channels (34). Opening these channels induces hyperpolarization, which attenuates the myogenic response by inactivating voltage-sensitive Ca^{2+} channels. Loutzenhiser and Parker demonstrated that hypoxia blunts myogenic reactivity of renal afferent arterioles, which is restored by glibenclamide (34). This further argues in favor of an involvement of K_{ATP} channels.

Adenosine, whose levels increase during hypoxia (2), cannot explain the hypoxia-induced autoregulation changes. TGF depends critically on adenosine (35); thus, increased adenosine production may also blunt autoregulation during hypoxia. However, adenosine acts as a vasoconstrictor in the renal cortex. This is not in line with the baseline RBF changes during hypoxia, nor does it agree with laser-Doppler flux in the cortex (Figures 2 and 3).

Restoration of RPP (Incremental Pressure Ramp)

The ramp-wise restoration of RPP exhibited similar differences in the levels of RBF, *i.e.*, hypoxia increased RBF whereas hyperoxia decreased RBF. Moreover, the autoregulatory response seems to occur at lower RPP levels during hyperoxia than for hypoxia. Baseline values of RBF, however, were reduced when compared with the decremental ramp. In nature and after successful treatment of severe hypotension, a reduction of RPP will be compensated for after some time. Nevertheless, only little is known about the reestablishment of RBF as perfusion pressure is restored. One study reported a long-lasting diminishing of RBF, GFR, and single-nephron GFR after restoring RPP (36). This is similar to a study by Olof *et al.* (18) and agrees with the effects depicted in Figures 2 and 3 of the present study. The data of the above-mentioned study (36) were interpreted in terms of an off-setting of TGF to lower values (75 to 80% of baseline). Thus, this may also explain our findings in the intact kidney of the conscious rat. However, our study was not designed to discern myogenic from TGF effects.

Conclusion

Different concentrations of inhaled O_2 influences renal vascular tone and alters kidney autoregulation. Outer medullary RBF, as estimated by laser-Doppler flux 4 mm below the renal

surface, is remarkably well maintained in the face of RPP reductions. Perhaps this reflects a fine-tuning of filtration, reabsorption, tissue oxygen, and flow. It is inferred that decreasing RPP below a certain value dilates efferent glomerular vessels, which reduces filtration and increases medullary blood flow. Thus, the solute load in the more distal nephron portions diminishes, leading to reduced O₂ demand. Moreover, a regional increase of RBF occurs in the outlying renal medullary layer, a nephron portion, which is particularly susceptible to hypoxia. When the inhaled oxygen concentration is reduced, the kidney fails to maintain these protective effects on outer medullary blood flow. In light of the present findings, it seems crucial to maintain sufficient inspiratory O₂ levels when RPP is low, e.g., during various forms of shock.

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