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ORIGINAL ARTICLE

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Intrarenal oxygen tension measured by a modified Clark electrode at normal and low blood pressure and after injection of x-ray contrast media

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Abstract The oxygen tension (pO_2) in the rat kidney was studied using a Clark microelectrode with a guard cathode behind the sensing cathode. The mean (± SEM) outer tip diameter of the electrodes used was 5.5 ± 1.9 μm. The zero-pO_2 current amounted to 12.5 ± 0.9 pA at 37°C; at air saturation it was 252 ± 22.9 pA. Rats with a systolic blood pressure (BP) above 80 mmHg (where 1 mmHg = 133 Pa) showed an average pO_2 in the cortex of 45 ± 2 mmHg and in the outer medulla of 31 ±1 mmHg. In rats with a BP below 80 mmHg a paradoxically high outer medullary pO_2 of 40 ± 4 mmHg was found, while the pO_2 in the cortex was 27 ± 4 mmHg. Changes in pO_2 were also noted in the renal cortex and outer medulla after intravenous injections of the x-ray contrast medium diatrizoate (370 mg iodine/ml). In rats with normal BP, injection of diatrizoate caused a slight fall in pO_2 in the renal cortex, from 42 ± 4 to 38 ±4 mmHg. In the medulla pO_2 decreased significantly from 34 ± 6 to 20 ±4 mmHg. Ringer's solution did not induce any changes.

Key words Renal medulla · Microelectrode · Acute renal failure · Hypotension

Introduction

Because of their size, large oxygen microelectrodes influence the measurements of oxygen tension (pO_2) in tissues, so that unstable and sometimes unreliable values may be obtained [4]. As changes in pO_2 in the renal medulla are considered to be of major importance in the acute renal failure (ARF) that may occur following injection of contrast media (CM) [7], there is a need for techniques that measure pO_2 changes in tissues. Our group has studied the changes in renal blood flow in the renal cortex and inner medulla with various techniques [28, 32, 33] after injection of CM. The moderate alterations in cortical flow correspond well to findings made by other investigators when measuring total renal blood flow [21]. In the inner medulla, we have found a decrease in blood flow after injection of CM [28, 32], and indirect methods indicate that there is a decrease in blood flow in the outer medulla following such injection [33]. In an attempt to determine whether these flow changes result in decreased tissue pO_2 we have used a modified Clark electrode [36] for measuring changes in pO_2 in renal tissues.

The modified Clark microelectrode (Fig. 1) has a second cathode (a guard cathode) placed behind the O_2-sensitive cathode in order to minimize the oxygen passing to the O_2-sensing cathode from the electrolyte reservoir. Such electrodes have previously been used in environmental research by Revsbech [36].

pO_2 was measured at different depths in the kidney in rats with a systolic blood pressure (BP) of 80 mmHg (where 1 mmHg = 133 Pa) or above (group A, n = 52) and in rats with BP below 80 mmHg (group B, n = 8). pO_2 in the cortex and outer medulla of normotensive rats (BP ≥ 80 mmHg) was then studied following injection of the hyperosmolar contrast medium (CM) diatrizoate (group C, n = 6) or Ringer's solution (group D, n = 7).

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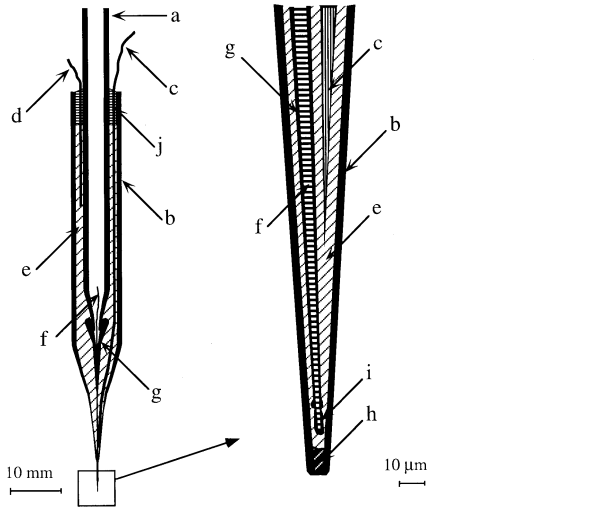
Materials and methods

Animals

The studies were performed on male Lewis-DA rats with an average body mass (BM) of 308 ± 7 g. The animals had free access to tap water and standard chow (R3, Ewos, Södertälje, Sweden containing 3 g sodium/kg, 8 g potassium/kg, 21% protein, 13 × 10^6



a. shaft of sensing cathode (Soda glass)
b. shaft of outer casing (Soda glass)
c. guard cathode (Ag)
d. reference cathode (Ag/AgCl)
e. electrolyte
f. platinum wire
g. glass encoating the pt-wire (Schott-glass 8533)
h. silicone membrane
i. goldplating of the platinum wire tip
j. epoxy resin

Fig. 1 The oxygen microelectrode with a guard cathode (modified from [36])

J/kg) up to the day of the experiment. They were anaesthetized with Inactin (Byk-Gulden, Konstanz, Germany), given intraperitoneally at a dosage of 100 mg/kg BM. Tracheostomy was performed and the rat was placed on a servo-controlled heating pad to maintain the body temperature at 37.5 °C.

Surgical procedures

A polyethylene catheter was placed in the left femoral artery for blood sampling and continuous monitoring of BP and in the left femoral vein for infusion of Ringer solution (0.5 ml/h per 100 g BM) composed of 120 mM NaCl, 2.5 mM KCl, 25 mM $NaHCO_3$ and 0.75 mM $CaCl_2$. The right femoral vein was catheterized for infusion of CM. The urinary bladder was catheterized for collection of urine. The left kidney was exposed by a left subcostal flank incision and immobilized in a plastic cup. The kidney was embedded in pieces of cotton wool soaked in Ringer's solution and its surface was covered with paraffin oil. During the experiment the temperature of the kidney was monitored with a thermocouple probe.

O_2 microelectrode

The O_2 microelectrode was a Clark-type electrode with a guard cathode as described by Revsbech [36]. The design of the electrode is shown in Fig. 1. The electrode is made of an outer casing of soda glass pulled at one end to an outer tip diameter of 5.5 ± 1.9 µm and an inner tip diameter of 2.1 ± 0.1 µm. The tip was filled with silicone rubber (Silastic, Medical Adhesive type A, Dow Corning, USA) which when cured formed a membrane (18 ± 6 µm thick). It is important to apply the silicone rubber solution within a few minutes after the tip is made (before the glass surface begins to hydrate), otherwise there will be a risk of leakage between the glass and the cured silicone plug, which will totally invalidate the use of the electrode for measurements in tissues.

Into the outer casing three electrodes were introduced, namely the O_2-sensitive cathode, the reference electrode and a guard cathode. The sensing cathode is made of a tapered platinum wire, with a tip diameter of 0.5–2 µm, melted into a fine glass capillary (Schott glass 8533, Schott Glaswerke, Germany). The naked, non-glass-encoated tip (length 4.2 ± 0.4 µm, diameter 3.0 ± 0.2 µm) of the platinum wire was gold-plated [5]. The glass-encoated platinum wire was then fused into a soda glass capillary. The tip of the O_2-sensitive cathode was placed 43 ± 4 µm from the silicone membrane in the tip of the outer casing. The guard cathode was made of 0.1-mm silver wire which was tapered at one end to a tip diameter of 1–2 µm. The tip of the guard cathode was placed at a distance of 471 ± 50 µm behind the sensing cathode. An Ag/AgCl wire was used as a reference anode. The electrolyte, consisting of 0.5 M KCl buffered with 0.05 M K_2CO_3 / 0.075 M $KHCO_3$ (pH 10.2), was injected into the outer casing. The electrode was then sealed with epoxy resin (Super Epoxy AB, Hisingeplast, Gothenburg, Sweden).

Functionally, the pO_2 electrode consists of two separate electric circuits. The platinum cathode and the silver anode make up the true pO_2 system, while the silver cathode and the silver anode form the guard system. Both circuits are supplied with –0.8 V from separate voltage sources and the current in the pO_2-sensitive circuit is recorded.

The polarographic method [18] is based upon the fact that a unique characteristic current/voltage curve is obtained when solutions of electro-oxidizible or electro-reducible substances are electrolysed in a cell. From such a current/voltage curve it is possible not only to identify, but also simultaneously to determine the concentrations of, the reducible or oxidizable substances present. The current/voltage relationship in a system for characterization of oxygen is represented by a sigmoid curve with a current plateau between –0.5 and –0.9 V. In this voltage range, the plateau current

Table 1 Characteristics of some oxygen microelectrodes

Electrode type	Outer diameter (tip) (µm)	Inner diameter (tip) (µm)	Silicone membrane length (µm)	Distance – membrane to cathode (µm)	Distance – cathode to guard cathode (µm)	N_2 with guard (pA)	N_2 without guard (pA)	Air, with guard (pA)	Air, without guard (pA)	90% response (s)	Stirring (%)
[1]	3	2	20	90	300	11	23	56	160	1	<1
[1]	4	2	30	20	1000	2	7	107	157	5	<1
[1]	4	3	120	20	600	18	78	361	553	40	<1
[2]	45	40	30	45	2000	22	62	1486	1625	4.7	3
[2]	18	15	18	30	300	12	209	632	1430	2	2.7
Average of 12 electrodes used in this study (1)	5.5±1.9	2.1±0.1	18±6	43±4	471±50	14.3±2.6	44±12	207±57	297±73	2.6±0.5	0.8±0.2

[1] Microelectrodes used in this study
[2] Microelectrodes constructed for comparison

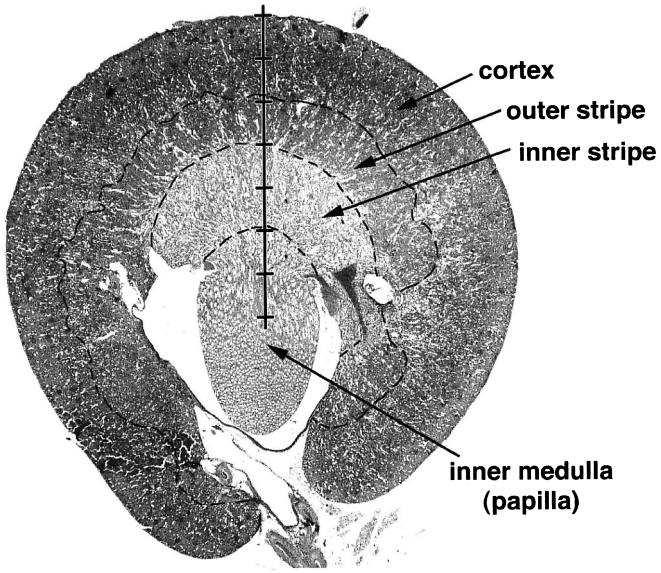


Fig. 2 A slice from a kidney of a 300-g Lewis-DA rat. The kidney was prepared with a conventional glutaraldehyde fixation technique [11]. The scale (in millimetres) refers to the distance from the kidney surface. The anatomical boundaries of the different parts of the kidney were marked in this photograph by Professor W. Kriz, Heidelberg, Germany

(diffusion current) depends on the pO_2 of the surrounding solution at the cathode surface. The oxygen will immediately be reduced (consumed) at the cathode surface, resulting in a current which is limited by the rate of oxygen diffusion to the cathode. This rate is limited by permeation factors in the electrolyte solution, in the membrane itself and in the medium outside the membrane [15]. This results in an electric current flow directly proportional to the partial pressure of oxygen [23]. Also, the steric design is of importance for the electrode function [15, 16]. Other redox systems in biological tissues can be excluded because of the impermeability of the silicone membrane. Other gases, such as CO_2, N_2 or NO, do not influence the electrode reactions at the electrode potential used.

The electrodes were calibrated in water at 37°C, saturated with N_2 or air, before and after the experiments. The picoamperemeters used were made by E. Larsen, Århus University, Århus, Denmark

Electrode characteristics

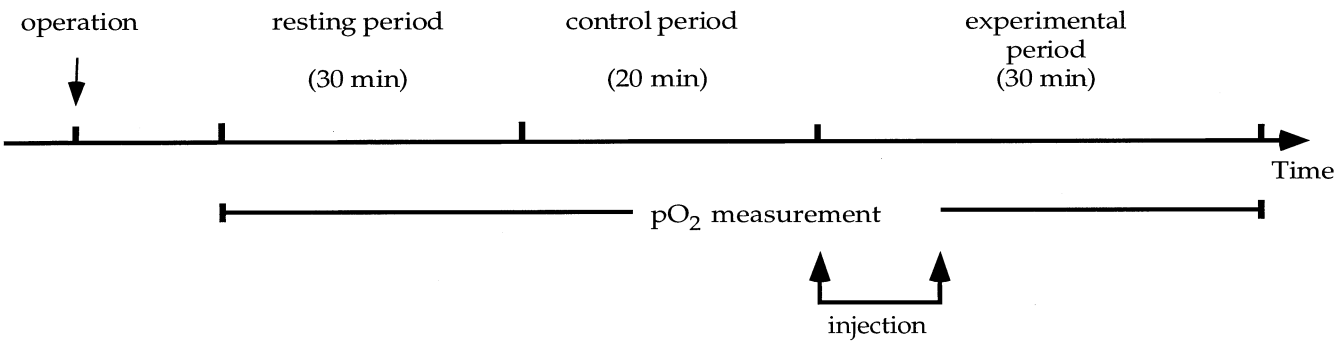
Table 1 gives examples of some electrode characteristics. The first electrodes were built in Århus by one of the authors (P.L.) and the rest were made in our laboratory in Uppsala. In the large number of electrodes used in the present study, the mean current at zero pO_2 amounted to 12.5 ± 0.9 pA at 37¡C. The current at air saturation was 252 ± 22.9 pA. The 90% response time was 2.6 ± 0.5 s. The stirring effect (change of electrode output in unstirred compared to stirred water) was 0.8 ± 0.2%. The average drift in the calibration of the electrodes from before to after the 2-h experiment was 1.0 ± 0.2% with N_2 gas and 1.9 ± 0.4% with air. The long-term stability of the electrodes was less than 0.5% drift per hour.

In total, 12 electrodes were tested (at 37°C) without and with polarization of the guard cathode. The electrodes had been polarized without the guard for at least 4 h before the guard cathode was polarized. The current of the sensing cathode in N_2 gas was found to be 44 ± 12 pA without the guard and 14.3 ± 2.6 pA with the guard. The current in air was 297 ± 73 pA without the guard and 207 ± 57 pA with the guard.

Experimental protocol

When the surgical procedure was completed, the animal was allowed to recover for 30 min. In 60 rats [group A (n = 52), BP ≥ 80 mmHg; group B (n = 8), BP < 80 mmHg] pO_2 was then measured at different levels in the kidney. The electrodes were inserted to different levels from the renal surface into the tissue with micromanipulators (Narishige, Japan) 1 mm at a time (Fig. 2). Depending on the response time of the electrode a steady-state pO_2 level was observed within 3–4 s at each level. The pO_2 was subsequently recorded as the average over 20 s at steady-state. In two other groups (C and D) pO_2 was measured simultaneously in the renal cortex and outer medulla (Fig. 3). After a 20-min control period, a 30-min experimental period started with an 8-min injection of CM or control substance. The rats in group C (n = 6) were given an injection of CM (diatrizoate 370 mgI/ml) (2070 mosmol/kg) (Urografin, Schering, Berlin, Germany). Diatrizoate was given at a dose of 1600 mg iodine/kg BM, a dose not unusual in angiographic practice. Ringer's solution (4.5 ml/kg BM) was used as a control (group D, n = 7). All solutions were at room temperature when injected. Throughout the experiment the pO_2 in the renal cortex and outer medulla and the blood pressure, body temperature and kidney temperature were recorded continuously with a MacLab Instrument (AD Instruments, Hastings, UK) connected to a Macintosh Power-PC 6100. In groups C and D, rats were excluded if the blood pressure fell below 80 mmHg. In these two groups pO_2 was measured at a depth of 1.0 mm in the cortex and at an average depth of 3.9 mm (range 3.5–4.5 mm) in the outer medulla (Fig. 2). After each experiment the average pO_2 over 1 min at the times 20, 15, 10, 5 and 1 min before injection of CM or control substance and at 1, 5, 10, 15, 20, 25 and 30 min after the start of this injection was calculated. At the end of the experiments, the microelectrodes were replaced by empty outer microelectrode casings with the same shape and size, placed on the same micromanipulator and inserted to the same depth. After injection of a small amount of India ink, the outer casings were removed and the kidney was sectioned in order to verify the sites of the measurements.

Fig. 3 Experimental protocol



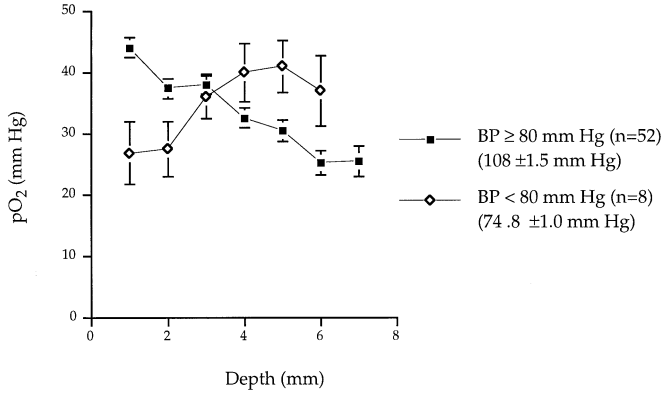


Fig. 4 Oxygen tension (pO_2) at different depths from the renal surface in normotensive rats rats (blood pressure (BP)≥80 mm Hg) and in rats with BP below 80 mm Hg

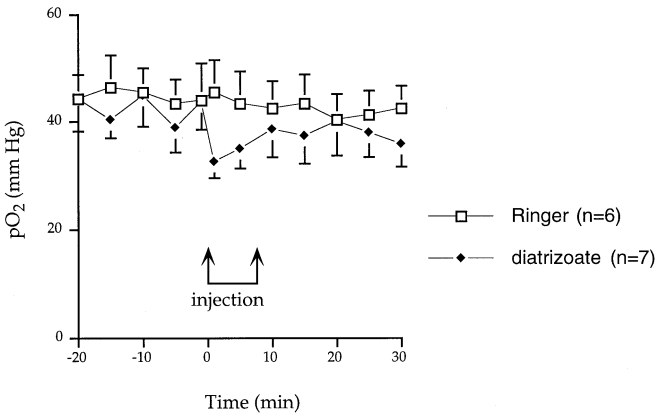


Fig. 5 Effects of injection of diatrizoate or Ringer's solution (control) on pO_2 (mm Hg) in the cortex

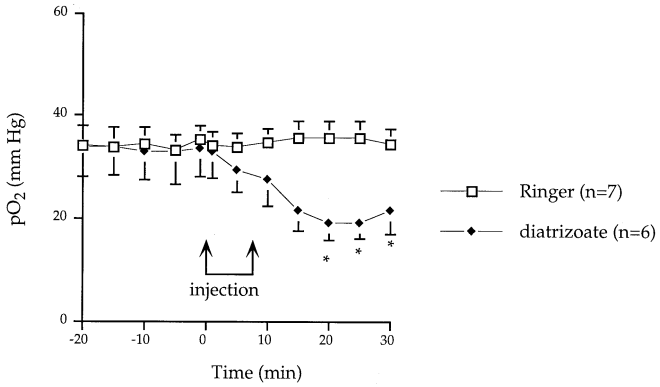


Fig. 6 Effects of injection of diatrizoate or Ringer's solution (control) on pO_2 (mm Hg) in the outer medulla. * Indicates a significant difference (P<0.05) compared with the control period

Blood and urine analysis

The urine volumes were measured gravimetrically. The urine sodium and potassium concentrations were measured by flame photometry (IL 543, Instrumentation, Milan, Italy). Urine osmolality was determined by the freezing-point depression method (Model 3MO, Advanced Instruments, Mass., USA). One urine sample was taken before and three were taken after CM injection. Blood samples were taken for haematocrit determination, once before CM injection and once after.

Statistical evaluation

Values are expressed as means ± SEM. The statistical significance of the data was tested with a multivariate analysis of variance (Manova) model, with comparison between results obtained during the control period and those obtained after drug administration (repeated measures). For comparing data between groups of animals a two-tailed Student's *t*-test for unpaired samples was applied. The JMP software from the SAS Institute was used. A *P* value of < 0.05 was accepted as significant (*) in all analyses.

Results

pO_2 at different depths in the kidney

BP above 80 mmHg

The pO_2 at different depths is depicted in Fig. 4. In the cortex (1 and 2 mm in from the surface) the pO_2 was 44 ±2 mmHg (range 8–88 mmHg). In the outer medulla (4–5 mm from the surface) it was 32 ± 2 (range 5–63) mmHg and in the inner medulla (6 and 7 mm in from the surface) it was 25 ±2 (range 3–46) mmHg. pO_2 was significantly higher in the cortex than in the medulla.

BP below 80 mmHg

In the cortex (1 and 2 mm in from the surface) the pO_2 was 27 ± 4 mmHg (range 15–49 mmHg). In the outer medulla (4–5 mm from the surface) it was 40 ± 4 (range 21–64) mmHg and in the inner medulla (6 and 7 mm in from the surface) it was 34 ±5 mmHg (range 13–55 mmHg). pO_2 was significantly lower in the cortex than in the outer medulla. In the cortex, pO_2 was significantly lower in rats with a BP below 80 mmHg than in those with BP above 80 mmHg. In the outer medulla, pO_2 was significantly higher in rats with a BP below 80 mmHg than in those with a BP above 80 mmHg.

pO_2 after injection of contrast medium

After injection of diatrizoate there was a slight, non-significant decrease in pO_2 in the cortex, from 42.4 ± 4.1 to 38.0 ± 4.3 mmHg (Fig. 5). In the outer medulla there was a significant decrease from 33.6 ± 5.8 to 19.9 ± 3.6 mmHg (Fig. 6). Ringer's solution caused no significant changes in the cortex or outer medulla. The kidney temperature remained constant throughout the experiment.

Urine data and haematocrit

The urine flow (UV) increased 51-fold after injection of diatrizoate (from 2.8 ± 0.7 to 144 ± 17 µl/min*). After Ringer injection it increased 1.5-fold (from 2.2 ± 0.2 to 3.4 ± 0.5 NS). Urine sodium output increased 68-fold after CM injection (from 0.09 ± 0.01 to

5.4 ± 1.1 μmol/min*), but only slightly after injection of Ringer (0.09 ± 0.03 to 0.11 ± 0.02 NS). Urine potassium output increased 25-fold in the CM group (from 0.235 ± 0.09 to 5.8 ± 1.1 μmol/min*) and 2.1-fold in the Ringer group (0.3 ± 0.08 to 0.63 ± 0.14 μmol/min*). Urine osmolality decreased after CM injection (from 1365 ± 178 to 608 ± 24 mosmol/kg*) but was increased in the Ringer group (2005 ± 240 to 2647 ± 132 mosmol/kg*). There was a slight increase in haematocrit after injection of CM (from 50 ± 0.5 to 53 ± 1.4%, NS) while in the Ringer group there was a slight decrease (from 52 ± 1 to 51 ± 1% NS).

Discussion

Our findings indicate that contrast media reduce the pO_2 in the outer renal medulla but leave that in the cortex unaffected. As in prior studies [3, 6, 8, 44], pO_2 was found to be lower in the renal medulla than in the cortex. However, in rats with arterial BP below 80 mmHg, pO_2 in the outer renal medulla was higher than that in the cortex.

In 1989 Revsbech [36] described a modified, miniaturized Clark electrode with an built-in guard cathode. This electrode has the advantage that all oxygen diffusing towards the sensing cathode is removed from the internal electrolyte reservoir. The zero-pO_2 current of the electric system remains low when the guard cathode is used, even though there is a large amount of electrolyte in the outer casing. The guard cathode did not otherwise alter the characteristics of the electrode. This O_2 microelectrode has a short stabilization period and the measurements performed in the kidney mostly show a stable value within a few seconds. Building the electrodes is a little bit tricky, but most electrodes show good stability, reproducibility and a short response time, and with gentle handling the same electrode can be used repeatedly for intratissue pO_2 measurements.

Several authors have studied the differences in pO_2 between various regions of the kidney. In the renal cortex the pO_2 is reported to vary considerably [6, 44], with values around 30–50 mmHg. In the outer medulla, values of about 20–35 mmHg have been reported and in the inner medulla the values have been found to range from 8 to 25 mmHg. We found higher values in the inner medulla than other investigators. This discrepancy might be explained by the diminutive size of our electrodes together with the construction of the electrodes with a guard cathode which reduces the current and hence the oxygen consumption. Furthermore, even though these electrodes have a small tip, the value obtained is an average from a certain tissue, and thus the lowest value may be lower than the measured one.

All electrodes inserted into tissues will to some extent affect the tissue [39]. In 1973 Albanese [1] showed mathematically that when measuring in tissues, an electrode with a tip of 1 μm has little error effect on pO_2 measurement, while a tip with an outer diameter of 10 μm will have a large error effect on this measurement. It is therefore important to use an electrode with a small tip diameter [29]. A large electrode will damage the tissue and compress the capillaries, resulting in a decreased pO_2. Further, a large electrode has a high diffusion current, reflecting a high oxygen consumption [38], and in tissues where the oxygen diffusion is lower than that in a fluid [5, 24, 40], this may affect the measurements, as the electrode is calibrated in water with diffusion characteristics different from those in tissues [4, 15, 16]. Despite the problem of obtaining absolute pO_2 values in tissues, these electrodes were built with a relatively large diffusion distance from the tip of the outer casing to the reducing sensing cathode. The difference between the readings in vigorously stirred and stagnant air-saturated water was thus only 0.8%, and the change in permeability when measuring in tissue will thus also have only a minor effect on the signal.

The lower pO_2 in the renal medulla compared to the renal cortex was first demonstrated by Aukland and Krog [3] in 1960. There are several explanations for this difference: (1) the counter-current vessel anatomy in the medulla [27], which allows diffusion of oxygen between the descending and ascending parts of the vasa recta; (2) the active, oxygen-consuming transport of sodium in the thick ascending limb of the loop of Henle (mTal) in the outer medulla; and (3) to a lesser extent the lower haematocrit in the inner medulla [42] through the skimming effect described by Pappenheimer et al. [22, 34].

After injection of the ionic hyperosmolar CM diatrizoate, we found a significant decrease in pO_2 in the outer medulla, while that in the cortex was not changed. There are several conceivable reasons for this decrease in the outer medulla. About 80% of the O_2 extraction from the blood in the kidney, the non-basal O_2 consumption, is directly proportional to the filtration rate [12, 25] and hence to the net reabsorption of sodium. As hyperosmolar CMs constitute osmotic diuretics, freely filtered by the glomeruli and poorly absorbed by the renal tubule, the high CM concentration in the tubule will reduce the reabsorption of water and sodium from the tubule and induce an osmotic diuresis. As a result of the osmotic effect, the amount of sodium arriving at mTal will increase, and hence also the active uptake from mTal [14, 35], leading to a further decrease in pO_2 in the outer medulla [45].

Another possible underlying cause of a decrease in pO_2 in the kidney is a decrease in blood flow. The renal vascular bed is unique in that it reacts to CM and hyperosmolar compounds with a biphasic response in renal blood flow [37] – first a vasodilatation with an increase in blood flow lasting less than 1 min, and then a prolonged vasoconstriction with a decrease in blood flow with a duration of several minutes. The mechanism of this unique vasoconstriction in the renal vessels is unknown, but several possibilities have been proposed, such as activation of the renin-angiotensin system [10] and an increase in endogenous intrarenal adenosine [2].

The blood flow may also be decreased by rheological effects. We have recently observed aggregation of red blood cells in the inner medullary vessels after injection of different CM [28]. Trapping (i.e. cessation of blood flow in capillaries due to tightly packed red blood cells) is another rheological phenomenon which has been

shown to occur in the outer medulla after injection of all types of CM [17, 31, 33].

The renal blood flow may also be decreased as a result of an elevation of intrarenal pressure due to the osmotic diuresis following injection of CM [20]. An intratubular obstruction [13] has also been suggested as a cause of an increase in intrarenal pressure and consequently a decrease in renal blood flow.

CMs are hyperviscous solutions – the more concentrated, the more viscous [30]. Excretion of CM into the tubules will therefore lead to an increased intratubular hydrostatic pressure [41]. This may cause a reduction in renal blood flow and hence a decrease in pO_2.

In eight rats we accidently found a BP of below 80 mmHg. These rats were all anaesthetized with the same dose of Inactin as were the other rats with normal BP. They had no major bleeding during the operation. Inactin may induce a low BP and this may be one explanation for the low BP in these animals. Brezis et al. [9] found that in rats with a BP below 80 mmHg, due to infusion of nitroprusside or controlled haemorrhage, the outer medullary pO_2, as in our study, was paradoxically high, while the cortical pO_2 was significantly lower than in the medulla. They also report that the increase in pO_2 in the outer medulla at a BP below 80 mmHg was abolished when furosemide was given prior to the haemorrhage. They consider this to indicate that the increase in pO_2 in the outer medulla in hypotension is due to decreased oxygen-consuming reabsorption of sodium in mTal following a decrease in glomerular filtration rate. These observations may also explain the finding by Leonhardt et al. [26] that in three patients in shock the urine pO_2 was high, whereas after treatment and a rise in BP the urine pO_2 decreased. This may partly also be explained by Ulfendahl's observation [43], i.e. that the haematocrit in the medulla was higher in cats with a low BP (< 75 mmHg) than in normotensive cats (BP > 75 mmHg). This was probably due to a decreased skimming effect [34]. Also in line with these results, Källskog et al. [19] reported that in rats with a low blood pressure (below 80 mmHg), the blood flow (measured by the microsphere technique) in the juxtaglomerular nephrons was increased compared with that in the outer cortex.

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