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Injection of low and iso-osmolar contrast medium decreases oxygen tension in the renal medulla

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Injection of low and iso-osmolar contrast medium decreases oxygen tension in the renal medulla. The oxygen tension (PO_2) in the renal cortex and outer renal medulla in 26 rats was studied by use of oxygen microelectrodes before and after injection of x-ray contrast media (CM). The CM, iopromide, ioxaglate and iotrolan were administrated intravenously in iodine equivalent doses (1,600 mg iodine/kg body wt). Ringer's solution was used as the control. In the outer medulla, all three CM induced a decrease in PO_2: iopromide ($N = 6$) from 30 ± 3 to 18 ± 4 mm Hg; ioxaglate ($N = 7$) from 32 ± 6 to 15 ± 4 mm Hg; and iotrolan ($N = 6$) from 36 ± 3 to 14 ± 4 mm Hg. All these decreases were significant. After the injection of Ringer's ($N = 7$) there was an increase from 34 ± 3 to 35 ± 3 mm Hg. In the cortex a slight decrease was noted after injection of CM, but this was significant only after injection of iotrolan. All tested contrast media decrease PO_2 in the outer renal medulla, which may partly explain contrast medium-induced acute renal failure.

Circulatory events in the renal medulla, eventually leading to medullary hypoxia, have been suggested as a possible mechanism underlying contrast medium-induced acute renal failure (CM-ARF). In previous studies we have found a reduction in renal medullary blood flow following injection of CM [1, 2]. In 1991 Heyman et al [3] reported that an injection of the high-osmolar contrast medium iotholamate led to a decrease in PO_2 in the outer renal medulla. After the introduction of the low-osmolar CM there was a hope that these compounds would be less nephrotoxic than the more hyperosmolar ones, and in a recent prospective study [4] iohexol was indeed found to have less influence on serum creatinine than diatrizoate. Even if there was no significant difference between these CM with respect to the occurrence of severe ARF (requiring dialysis), the meta-analysis of Barrett and Carlisle [5] indicated that use of low-osmolar contrast media may also prevent severe changes in renal function in patients with pre-existing renal function. In this study we have tested the hypothesis that the low and iso-osmolar CM also decrease PO_2 in the outer medulla.

The CM investigated were ioxaglate (ionic ratio 3.0), iopromide (nonionic ratio 3.0), and iotrolan (nonionic ratio 6.0) (Table 1).

Key words: Contrast media, oxygen tension, kidney, medulla, hypoxia, acute renal failure, radiocontrast toxicity.

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METHODS

Animals

The studies were performed on 26 male Lewis-DA rats with an average body wt of 293 (± 4) g. The animals had free access to tap water and standard chow containing 3 g Na/kg, 8 g K/kg, 21% protein and 13×10^6 Joule/kg (R3, Ewos, Södertälje, Sweden), up until the day of the experiment. They were anesthetized with Inactin® (Byk-Gulden, Konstanz, Germany), given intraperitoneally at a dose of 120 mg/kg body wt. 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 monitoring of blood pressure. The left femoral vein was catheterized for infusion of Ringer solution (0.5 ml/hr/100 g body wt) 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 sub-costal flank incision and immobilized in a plastic cup. The kidney was embedded in pieces of cotton wool soaked in Ringer solution and its surface was covered with paraffin oil. During the experiment the temperature of the kidney was monitored with a thermocouple probe.

Oxygen microelectrode

The oxygen microelectrodes used in this study were modified Clarke-type [6] electrodes, constructed as described by Revsbech [7] and used in the kidney as described in a previous report [8]. They had a tip diameter of 2 to 8 μm and an inner luminal diameter at the tip of 1 to 2 μm. The electrodes were polarized at −0.800 V, an electrical potential in which a linear response is observed between the oxygen tension and the electrode current. The current was measured by pico-amperemeters (University of Aarhus, Denmark). The electrodes were calibrated in water at 37°C bubbled with N_2 gas or air before and after the experiments. The electrode current in N_2 gas was 10 (± 1.1) pA, and in air 239 (± 28) pA. The stirring effect in bubbling water was 1.3% (± 0.3).

Table 1. Tested substances

Substance	Type of contrast medium	Iodine conc. *mg/ml*	Osmolality *mOsm/kg*
Iopromide[a] (Ultravist®)	Non-ionic Monomer	370	774
Ioxaglate[a] (Hexabrix®)	Ionic Dimer	320	580
Iotrolan[a] (Isovist®)	Non-ionic Dimer	300	320
Ringer	—	0	310

[a] Data are from the manufacturer

Experimental protocol

When the surgical procedure was completed, the animal was allowed to recover for 30 minutes. Subsequently, after a 20-minute control period, a 30-minute experimental period started with an eight minute injection of CM or control substance (Fig. 1.). The CM tested were: iopromide, 370 mg/ml (Ultravist®; Schering, Berlin, Germany); ioxaglate, 320 mg/ml (Hexabrix®; Laboratories Guerbet, Aulnay-sous-Bois, France) and iotrolan, 300 mg/ml (Isovist®; Schering). All CM were given in a dosage of 1,600 mg iodine/kg body wt, which is about 5 ml CM/kg body wt of a 300 mg I/ml CM in a 60 kg person. Such doses are not unusual in angiographic practise. Ringer's solution was used as a control (Table 1). All solutions were at room temperature when injected. Throughout the experiment the oxygen tension 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. The oxygen tension (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 to 4.5) in the inner stripe of the outer medulla. After each experiment the average PO_2 for one minute at the times 20, 15, 10, 5 and one minute before injection of CM or control substance and 1, 5, 10, 15, 20, 25 and 30 minutes after this injection was analyzed. 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 micro-manipulator and inserted at 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 that the measurements had been made at the intended sites, that is, in the cortex and in the inner stripe of the outer medulla. If it was found that the tips of the microelectrodes had not been in the appropriate places, the measurements were excluded.

Blood and urine analysis

The urine volumes were measured gravimetrically. The urine sodium and potassium concentrations were measured by flame photometry (IL 543; Instrumentation Lab, Milano, Italy). Urine osmolality was determined by the freezing point depression method (Model 3MO; Advanced Instruments, Lexington, MA, USA). One urine sample was taken before injection of CM and three samples after this injection. Blood samples for hematocrit measurement were taken before and after injection of CM.

Statistical evaluation

Values are expressed as means ± SEM. The statistical significance of the data were tested by using a multivariate analysis of variance (MANOVA) model, comparing results obtained during the control period with those obtained after drug administration (repeated measures). For comparison of data between groups of animals a two-tail Student's *t*-test for unpaired samples was applied. The JMP software from the SAS Institute was used [9]. A P value of < 0.05 was accepted as significant in all analyses.

RESULTS

Oxygen tension in the cortex

As seen in Table 2 and Figure 2, all CM induced a slight decrease in PO_2 in the cortex. This decrease was not significant in the ioxaglate or iopromide groups. In the iotrolan group it was significant 15 and 20 minutes after the injection, but not subsequently. Ringer caused no significant changes.

Oxygen tension in the medulla

All CM induced a significant decrease in PO_2 in the outer medulla: iopromide ($N = 6$) from 30 ± 3 to 18 ± 4 mm Hg; ioxaglate ($N = 7$) from 32 ± 6 to 15 ± 4 mm Hg; and iotrolan ($N = 6$) from 36 ± 3 to 14 ± 4 mm Hg. No significant difference was found between the tested CM. After injection of Ringer ($N = 7$) there was an increase from 34 ± 3 to 35 ± 3 mm Hg (Table 2 and Figure 3).

Urine and blood data

The results are summarized in Table 3. Urine flow increased from 21- to 28-fold after injection of ioxaglate and iopromide. After iotrolan injection it increased threefold and after injection of Ringer's 1.5-fold. Urine sodium output increased 13- to 43-fold after iopromide and ioxaglate injection and 1.7-fold after injection of iotrolan, respectively. The increases in urine flow and urine sodium excretion were significant in all but the Ringer group. Urine potassium output increased 6- and 27-fold after injection of iopromide and ioxaglate, respectively, and 2.1-fold after Ringer injection. All these increases were significant. In the iotrolan group there was only a slight nonsignificant increase after the injection. Urine osmolality decreased significantly in all groups except the Ringer group. There was no change in hematocrit in any of the groups.

DISCUSSION

During the last decade, new, less hyperosmotic and more expensive contrast media have been introduced. These have brought an improvement for the patients in that they cause less discomfort [10]. In patients with normal renal function, the risk of developing ARF after injection of contrast media is equally low with both low and high osmolar contrast media [5]. In several recent studies [4, 5, 11–14] it has been found that renal function, when monitored in terms of creatinine clearance or serum creatinine, is affected less by injections of low-osmolar CM than by high-osmolar CM. Nevertheless, no study has yet shown any statistical difference concerning the incidence of severe acute renal failure (requiring dialysis) between high and low osmolar CM, though the meta-analysis of Barrett and Carlisle indicated that use of low osmolar contrast media may also prevent severe changes in renal function [5].

In 1991 Heyman et al [3] observed a decrease in PO_2 in the renal outer medulla in salt-depleted uninephrectomized rats following injection of the ionic, hyperosmolar monomeric contrast medium iotholamate. They found a PO_2 level of 26 ± 3 mm Hg in

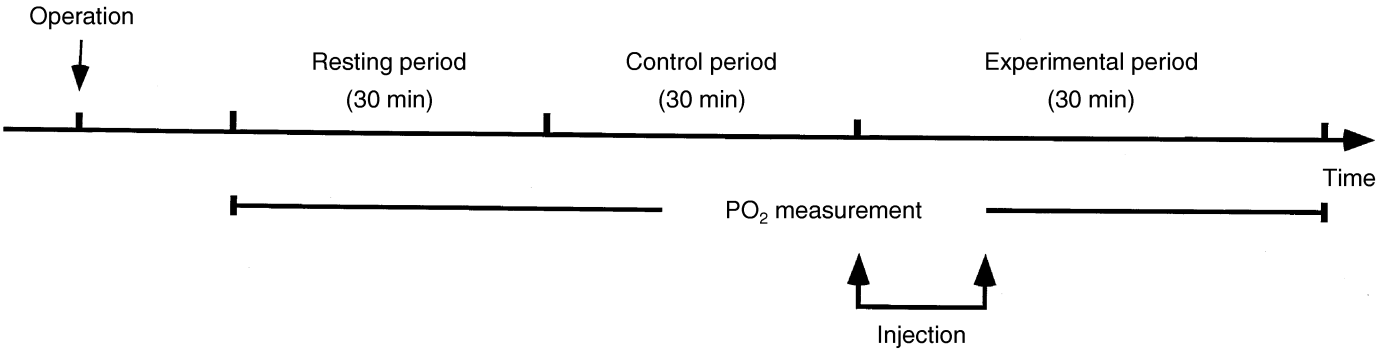

Fig. 1. Experimental protocol.

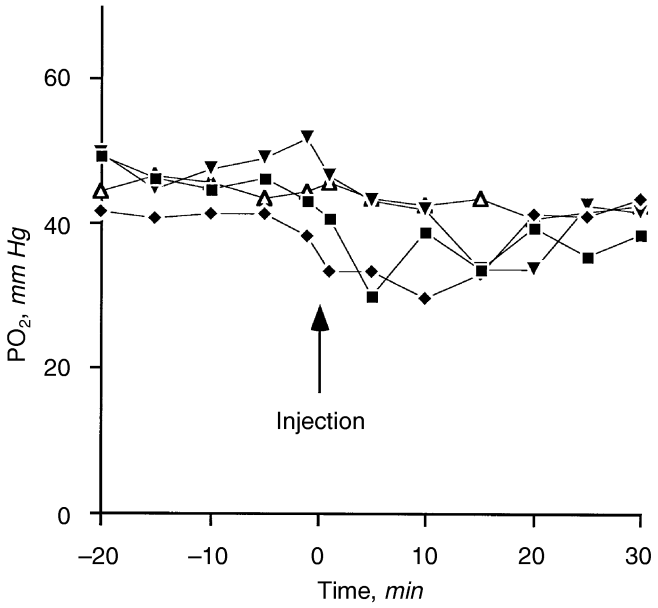

Fig. 2. Effects of injection of different contrast media and Ringer solution (control) on PO_2 (mm Hg) in the renal cortex. Symbols are: (■) ioxaglate (N = 7); (◆) iopromide (N = 6); (▼) iotrolan (N = 6); (△) Ringer's solution (N = 7).

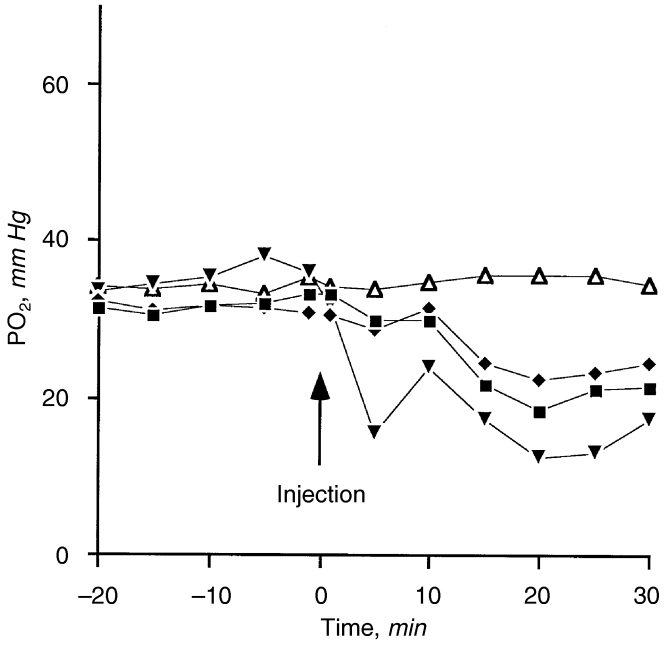

Fig. 3. Effects of injection of different contrast media and Ringer solution (control) on PO_2 (mm Hg) in the renal medulla. Symbols are: (■) ioxaglate (N = 6); (◆) iopromide (N = 7); (▼) iotrolan (N = 6); (△) Ringer's solution (N = 7).

the inner stripe of the outer medulla and after injection of iothalamate they noted levels of 9 ± 2 mm Hg. On an average the reduction in PO_2, seen in Heyman et al's study [3] is similar to that in the present study. A PO_2 level of about 10 mm Hg is not necessarily harmful. The normal PO_2 in the muscle is about 10 mm Hg [15]. However, in the outer medullary region, with its high metabolic activity, a decrease may be injurious, as indicated by the morphological correlate to the decrease in PO_2 in the outer medulla reported by Alcorn et al [16], who described a specific lesion in the cells of the thick ascending limb (mTAL) of the loop of Henle, in the outer medulla, characterized by features ranging from mitochondrial swelling to nuclear pyknosis and cell death in renal *in vitro* perfusion studies. These findings were confirmed by Brezis et al [17–19], who found that the more severe the ischemia the more pronounced the injury and that the injury decreased in severity in kidneys given a high oxygen supply.

The reduction in PO_2 in the outer medulla after injection of CM may be explained by different mechanisms. As hyperosmolar compounds, CM act as 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 [20], leading to a further decrease in PO_2 in the outer medulla [3, 21–23]. As seen in Table 3, in our study significant natriuresis occurred after injection of all CM, although the natriuresis caused by iotrolan was only about one-tenth of that produced by ioxaglate and iopromide. This indicates that this explanation for a decrease in PO_2 is not plausible in the case of iotrolan.

Another possible mechanism underlying a decrease in PO_2 in the kidney is a reduction in blood flow. All major vascular beds, except in the kidney, respond to CM and hyperosmolar compounds with a transient vasodilation [24]. The blood flow may be

Table 2. Oxygen tension (PO_2, mm Hg) in the renal cortex and outer medulla before (control value) and after injection of contrast media

	Ioxaglate ($N = 7$) (Hexabrix®)	Iopromide ($N = 6$) (Ultravist®)	Iotrolan ($N = 6$) (Isovist®)	Ringer ($N = 7$)
Renal cortex				
PO_2 before CM	45 ± 5 (100%)	43 ± 7 (100%)	50 ± 4 (100%)	45 ± 5 (100%)
PO_2 after CM[a]	38 ± 2 (84%)	40 ± 4 (93%)	38 ± 5 (76%)[b]	41 ± 4 (91%)
Outer medulla				
PO_2 before CM	32 ± 6 (100%)	30 ± 3 (100%)	36 ± 3 (100%)	34 ± 3 (100%)
PO_2 after CM[a]	15 ± 4 (47%)[b]	18 ± 4 (60%)[b]	14 ± 4 (39%)[b]	35 ± 3 (103%)

Ringer's solution was used as the control. Percentages are relative values. Control level is 100%.
[a] Average of the three last observations (20, 25 and 30 min) after CM or Ringer's solution
[b] Indicates a significant difference ($P < 0.05$) compared with the control period

Table 3. Effects of injection of different contrast media (CM) and Ringer's solution on urine flow, sodium excretion, potassium excretion, urine osmolality and hematocrit

	Ioxaglate ($N = 7$) (Hexabrix®)	Iopromide ($N = 6$) (Ultravist®)	Iotrolan ($N = 6$) (Isovist®)	Ringer's ($N = 7$)
Urine flow *μl/min*				
Before CM	2.1 ± 0.2	3.2 ± 0.9	2.8 ± 0.5	2.2 ± 0.2
After CM[a]	59.4 ± 9.9[b]	71.1 ± 3.0[b]	9.1 ± 2.9[b]	3.4 ± 0.5
Sodium excretion *μmol/min*				
Before CM	0.07 ± 0.01	0.08 ± 0.02	0.13 ± 0.05	0.09 ± 0.03
After CM[a]	3.0 ± 0.28[b]	1.03 ± 0.21	0.22 ± 0.08[b]	0.11 ± 0.02
Potassium excretion *μmol/min*				
Before CM	0.16 ± 0.05	0.27 ± 0.07	0.34 ± 0.12	0.30 ± 0.08
After CM	4.4 ± 0.49[b]	1.67 ± 0.14[b]	0.35 ± 0.09	0.63 ± 0.14[b]
U_{Osm} *mOsm/kg*				
Before CM	1747 ± 184	1813 ± 170	2403 ± 374	2005 ± 240
After CM[a]	819 ± 48[b]	845 ± 41[b]	967 ± 267[b]	2647 ± 132[b]
Hematocrit %				
Before CM	51 ± 1	50 ± 1	50 ± 1	52 ± 1
After CM[a]	53 ± 1	51 ± 1	52 ± 1	51 ± 1

[a] Maximal change
[b] Significantly difference ($P < 0.05$) compared with the control period

decreased by rheological effects. We have recently observed aggregation in inner medullary vessels [2]. Trapping (that is, cessation of blood flow in capillaries due to tightly packed red blood cells) is another rheological phenomenon that has been shown to occur in the outer medulla after injection of all types of CM [2, 25]. In the inner medulla [1, 2], we found that the nonionic CM decreased the blood flow and induced aggregation to a greater extent than the ionic CM ioxaglate. In the case of all CM, red blood cell aggregation and trapping may have contributed, either directly or indirectly, to a decrease in blood flow to the PO_2 reduction seen in the present study.

Osmotic diuresis with a highly increased urine flow, distending the tubules and collecting ducts may lead to renal swelling and a rise in intrarenal venous pressure [26], resulting in a decrease in blood flow. In our study, this mechanism may be valid for the compounds causing pronounced diuresis and hence less valid for iotrolan (Table 3).

Contrast media (CM) are hyperviscous solutions, that is, the more concentrated, the more viscous. The new, iso-osmotic nonionic dimer iotrolan, which because of its isotonicity results in the least diuresis (Table 3), will consequently appear in the highest concentration in the tubules. This will lead to a high intratubular viscosity, the resulting viscosity also being a consequence of the large size of the dimeric iotrolan molecule. This has been shown by Ueda et al [27] to result in an extremely high intratubular hydrostatic pressure. We propose that by this action iotrolan may reduce renal blood flow, secondary to an increase in intrarenal pressure and consequently a decrease in PO_2. As an iso-osmotic agent, iotrolan will be concentrated in the tubules, and despite having a low LD_{50} [28] it will be in a more concentrated form than other CM with higher LD_{50}, which may affect the local cells. The increase in osmolar excretion after iotrolan-injection was only 30%, but despite this there was a marked decrease in urine osmolality (U_{Osm}). In the ioxaglate and iopromide groups the osmolar excretion increases are 13-fold and 10.3-fold and after Ringer injection twofold. Concerning the ioxaglate and iopromide compounds their effect on U_{Osm} may be explained by their diuretic action, with the iotrolan compound this cannot be the case, as iotrolan has a low diuretic effect. Thus, a functional impairment secondary to hypoxia in the thick ascending limb of the loop of Henle may be an explanation for this inability to concentrate the urine.

Other possible contributors to a decrease in renal blood flow in response to administration of CM are increases in calcium [29], adenosine [14, 30] and endothelin [31], and decreased production of nitric oxide [32]. These parameters were not measured in the present study and, thus, the extent to which these mechanisms might have influenced the results cannot be determined.

Agmon et al have reported an increase in outer medullary blood flow, measured by laser-Doppler probes, following injection

of iothalamate [33] given in a dose of 2.900 mg I/kg body wt during two minutes. These findings may be explained if the higher metabolic demand increased out of proportion to the increase in blood flow. Other studies have demonstrated outer medullary trapping of red blood cells following the administration of contrast media [3, 34], indicating that there is a decrease in blood flow in the outer medulla after CM injection.

These experimental observations that, analogously to high-osmolar CM, the low-osmolar and iso-osmolar CM induce a decrease in PO_2 in the renal medulla, thus indicate that hypoxia in the medulla may explain the acute renal failure seen after administration of these compounds.

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