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# Effect of iodinated contrast media on the oxygen tension in the renal cortico-medullary of pigs

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## Abstract

Repeated injections of iodinated contrast media (CM) can lead to a deterioration of the renal blood flow, can redistribute blood from the renal cortex to other parts of the kidney and can cause small decreases of the blood flow in cortical capillaries, a significant reduction in blood flow in peritubular capillaries, and a significant reduction in blood flow in the vasa recta. Therefore, a study in pigs was designed, to show whether the repeated injection of CM boli, alone, can cause a reduction of oxygenation in the cortico-medullar renal tissue – the region with the highest oxygen demand in the kidney - of pigs.

While the mean $pO_2$-value had only decreased by 0.3 mmHg from 29.9 ± 4.3 mmHg to 29.6 ± 4.3 mmHg ($p$=0.8799) after the tenth Iodixanol bolus, it decreased by 5.9 mmHg from 34.0 ± 4.3 mmHg to 28.1 ± 4.3 mmHg after the tenth Iopromide bolus ($p$=0.044). This revealed a remarkable difference in the influence of these CM on the oxygen partial pressure in the kidney.

Repeated applications of CM had a significant influence on the renal oxygen partial pressure. In line with earlier studies showing a redistribution of blood from the cortex to other renal areas, this study revealed that Iodixanol – in contrast to Iopromide - induced no changes in the $pO_2$ in the cortico-medullar region, which confirms that

Iodixanol did not hinder the flow of blood through the renal micro-vessels. These results are in favor of a hypothesis from Brezis that a microcirculatory disorder might be the basis for the development of CI-AKI.

Key words: Contrast agent, Iodixanol, Iopromide, tissue oxygen partial pressure, CI-AKI, contrast-induced acute kidney injury

## 1. Introduction

Iodinated contrast media (CM) are being widely utilized for diagnostic and therapeutic purposes. The increasing numbers of coronary interventions in an aging population and the increasing procedural complexity have resulted in greater numbers of renal impairments associated with the exposure to CM, a disorder described as contrast-induced acute kidney injury (CI-AKI) [1-3]. Most cases of CI-AKI seem to be reversible and are associated with a mild and transient impairment of renal function [4]. But CI-AKI is also associated with a risk for short- and long-term haemodialysis, and increases the mortality rate up to 36% with survival rates of 19% after 2 years. By definition, CI-AKI manifests as an abrupt decline in renal function within 3 days after CM administration in the absence of an alternative aetiology [5-8]. It is characterized by an increase in the serum creatinine (SCR) level of at least 0.5 mg/dl (> 44.2 µmol/l) or 25% as compared to baseline values [9].

The pathogenesis of CI-AKI is still uncertain. It has been ascertained that the application of some CM is quickly followed by changes in morphology of erythrocytes and endothelial cells. Three minutes after immersion of erythrocytes in mixtures of different CM with autologous blood plasma the red blood cells could be transformed completely into echinocytes, depending on the type of CM used [10-13]. These changes in morphology coincided with a considerable increase in cell rigidity, associated with a hindrance of erythrocytes in the capillary passage [14, 15]. An increase in endothelial thickness was described also, depending on the type of CM used [16]. The increase in endothelial thickness is caused by a buckling of the endothelial cells into the capillary lumen, which in the case of Iopromide resulted in a 70% decrease of the free capillary lumen. Both of the reported alterations are assumed to generate a deterioration of capillary perfusion.

In mice and rats, a disorder in the renal microcirculation following the application of CM has been ascertained, already [9, 17, 18]. These rodents, however, which can extremely concentrate their urine, have a somewhat different kidney anatomy making it difficult to transfer results, obtained in these animals, to large animals like pigs or even to humans [19]. Very recently, Lamby et al. could show that i) the repeated application of CM can lead to deterioration of the renal blood flow, ii) that CM can

redistribute blood from the renal cortex to other parts of the kidney and iii) that there were small decreases of the blood flow in cortical capillaries, iv) a significant reduction in blood flow in peritubular capillaries and v) a significant reduction in blood flow in the vasa recta [20]. Are there consequences of this redistribution and disorder of the microperfusion?

Therefore, a study in pigs was designed, to show whether one of the discussed critical factors alone, the repeated injection of CM, can cause a reduction of oxygenation in the cortico-medullar renal tissue – the region with the highest oxygen demand in the pig kidney - of large animals, of young and healthy pigs [21-23].

## 2. Material and Methods

### *2.1 Study design*

The study was performed as a prospective, randomized examination to compare the effects of two CM (Iodixanol vs Iopromide) applied in $n$ = 16 piglets (sus scrofa domesticus). A detailed description of the study design was published earlier [20]. Group I received Iodixanol randomly attributed to $n$ = 8 animals, group II received Iopromide randomly assigned to $n$=8 animals. Simulating the clinical procedure, each animal received a total of 10 injections into the aorta, either with 5 ml Iodixanol per injection or with 4.32 ml Iopromide per injection, at a volume rate of 10 ml/sec, so that both groups received equal amounts of iodine [23]. The 10 injections were applied in the suprarenal part of the distal abdominal aorta. Five minutes passed between two injections. Each animal received a total of 500 ml NaCl throughout the entire examination, which also follows the clinical procedure. All examinations were carried out under general anesthesia, which was administered by a board-certified anesthetist with great experience in pig anesthesia. The Bavarian Institutional Animal Care and Use Committee approved the study protocol for the experiments performed in this study (number: 54-2532.1-31/13). All procedures were carried out in accordance to the EU Directive 2010/63/EU for animal experiments.

### *2.2 Iodinated contrast media*

Two standard CM were applied. Iodixanol 320 mg Iodine/ml, GE Healthcare, München, Germany, and Iopromide 370 mg Iodine/ml, Bayer/Schering, Berlin, Germany (Table 1).

Table 1: Iodine concentration and osmolality for Iodixanol and Iopromid

| Contrast agent | Iodine concentration [mg/ml] | Osmolality [mOsmol/kg $H_2O$] |
|---|---|---|
| Iodixanol (Visipaque ™) | 320 | 290 |
| Iopromid (Ultravist ™) | 370 | 770 |

*2.3 Surgical access to the kidney*

The animals were placed on their back with a slight hyper-extension of the lumbar spinal column. After sterile lavage and coverage of the non-operated regions, surgical access was gained through median laparotomy. Taking care not to endanger the intestine, the rectus sheath and the peritoneum were severed. Then the small intestine and the colon were dislocated outside the body. Trans-peritoneal access was gained and the v. cava, aorta, renal blood vessels and the ureter of the right kidney were identified. Following the ureter cranially, the renal hilus was identified, the kidney remained *in situ*, but fatty tissues and the fibrous capsule were removed from the lateral convex border and from the ventral parts of the kidney so that access for the $pO_2$ microcatheter and the ultrasound head was granted.

*2.4 Tissue oxygen partial pressure measurement*

The flexible $pO_2$ Clarke-type microcatheter was used for the continuous measurement of the oxygen partial pressure in the corticomedullary region (Integra Neuroscience, Germany) [24, 25]. The $pO_2$ microcatheter was inserted into the kidney using a sluice canula (20-Gauge catheter) by a specialist experienced in placing microcatheters in renal tissues according to Lübbers [26]. The $pO_2$ sensitive surface of the microcatheter (7.85 $mm^2$) was then – Ultrasound-guided - positioned in the corticomedullary region, which was verified by radiography after explantation (see Figure 1). The sluice canula

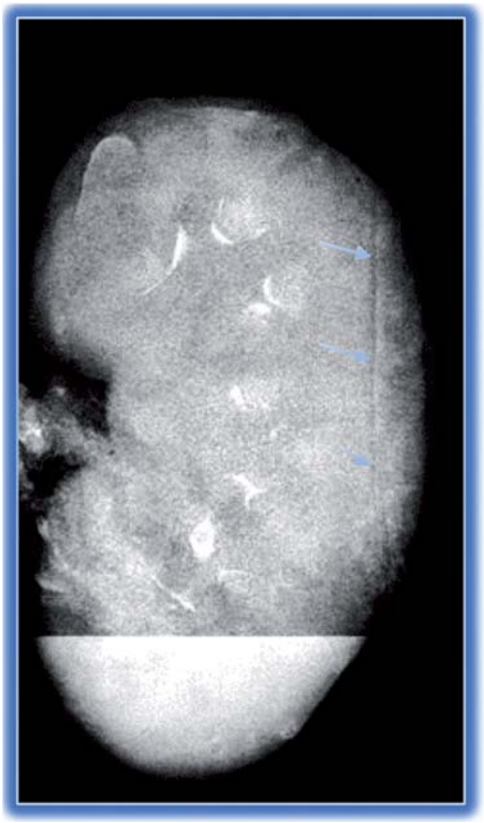

Fig. 1. Radiography of the explanted kidney. The channel of the $pO_2$ catheter is marked by the three arrows.

was removed and the microcatheter was immobilized on the kidney surface to prevent movements of the microcatheter. All measurements were performed after adaptation to room temperature.

*2.5 Statistics*

All samples are described by arithmetic means and standard deviations. An ANOVA for repeated measures was performed to analyze the influence of both contrast media on the tissue oxygen tension. *p*-values less than 0.05 were considered significant.

## 3. **Results**

The intra-renal oxygen partial pressure did not differ between both groups before CM administration ($p = 0.619$), so that homogeneity of the baseline parameters was given. The time course over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups after the first bolus of both CMs is shown in Figure 2.

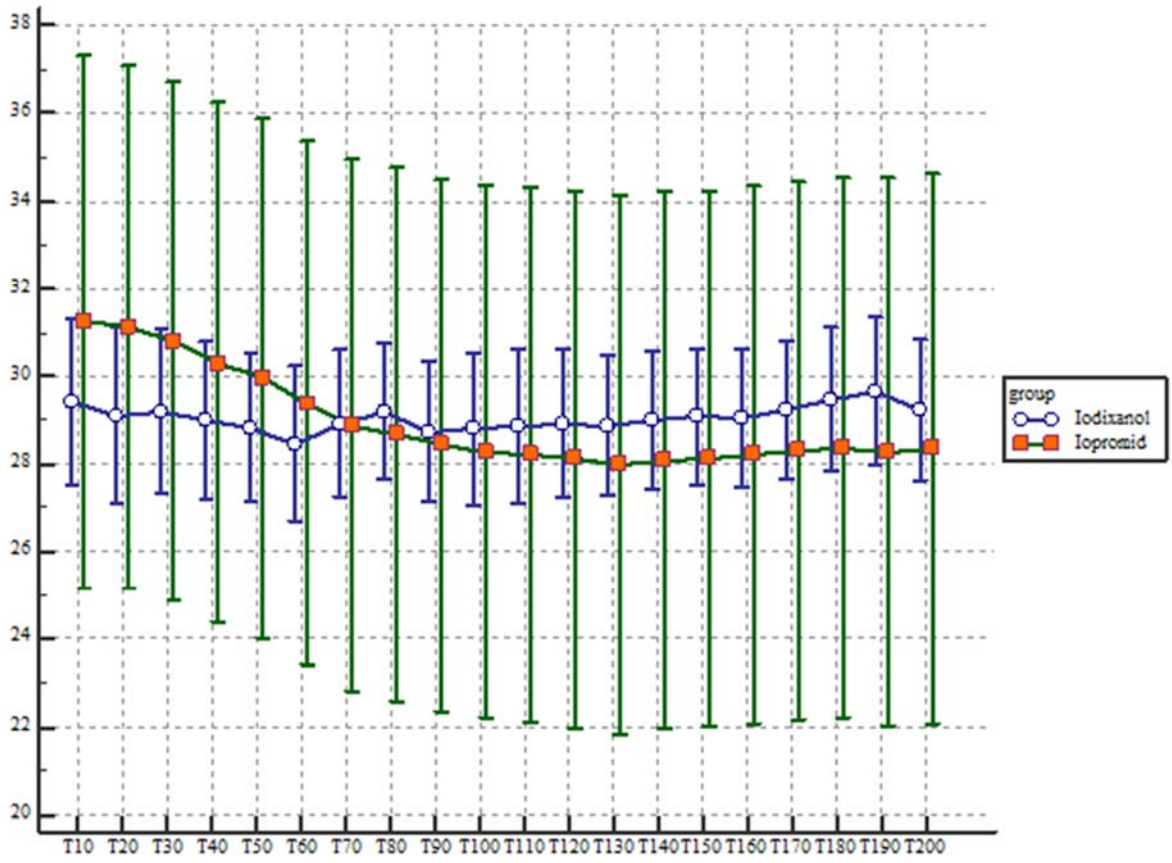


**Fig. 2**: Time course over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups after the first bolus of both CMs.

The injection of a bolus of 4.32 ml of Iopromide into the suprarenal aorta of animals induced a decrease of the mean renal $pO_2$ in tendency (Figure 2). 110 seconds after the

injection of Iopromide into the suprarenal aorta, the mean $pO_2$ in the outer medulla had decreased by 15 % compared to baseline values ($p < 0.0748$). After the injection of Iodixanol the mean $pO_2$ in the outer medulla remained unchanged.
Considering all results, the time courses of the mean $pO_2$ values in the outer renal medulla of both animal groups significantly differed between the two CM applied (ANOVA, Greenhouse-Geisser test: $p = 0.035$).
After the fifth bolus neither changes in the Iodixanol nor in the Iopromide group were found in the intrarenal $pO_2$ values (Figure 3). Both pO2 courses did not differ from one another ($p = 0.713$).

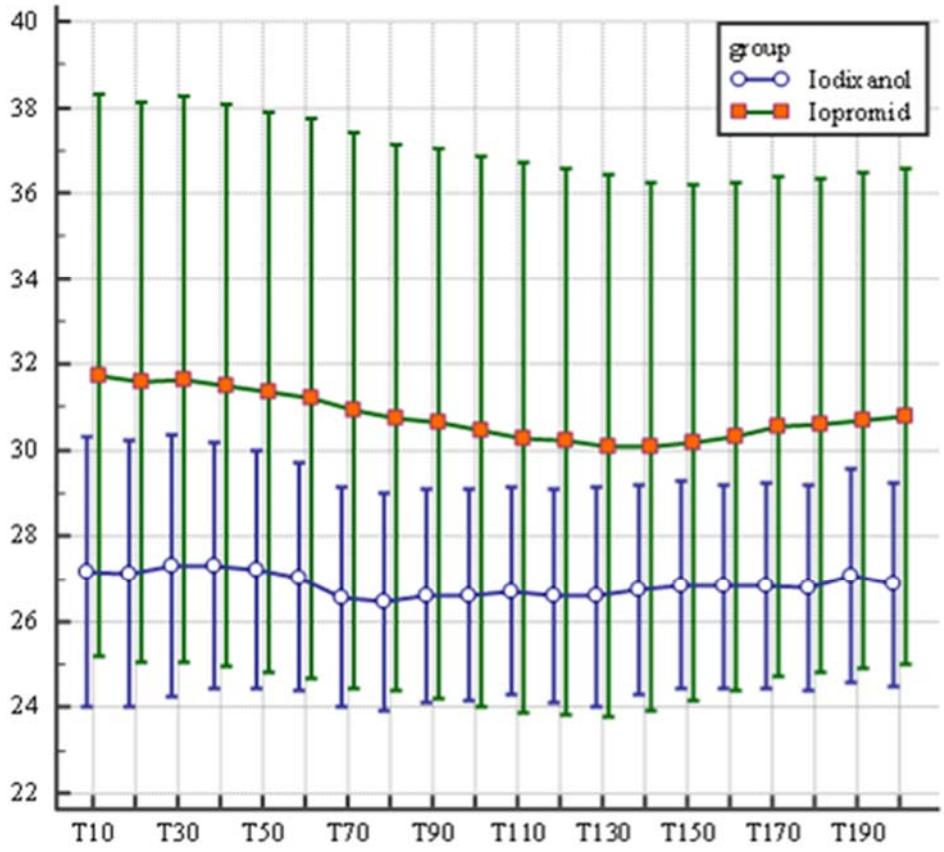


**Fig. 3**: Time course over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups after the fifth bolus of both CMs.

The time course over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups after the tenth bolus of both CMs is shown in Figure 4.

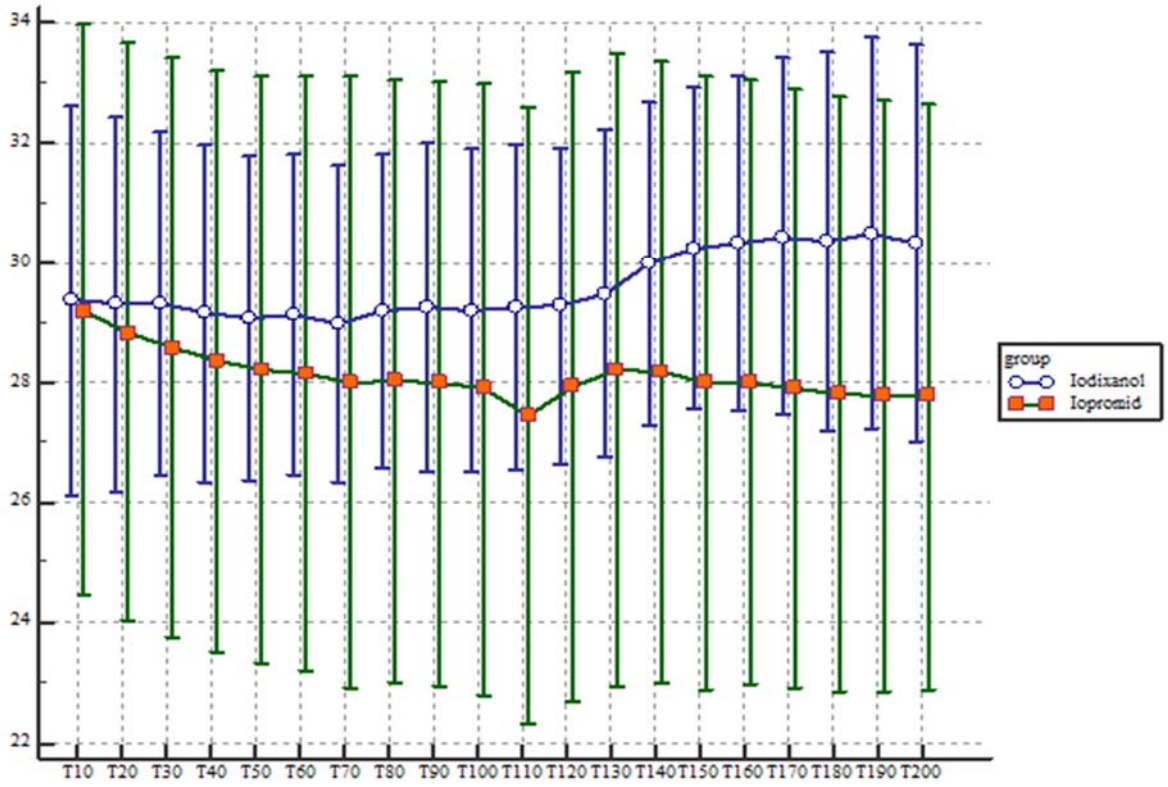


**Fig. 4**: Time course over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups after the tenth bolus of both CMs.

While the intra-renal $pO_2$-values showed a tendency to increase after Iodixanol injection (no negative influence of Iodixanol on $pO_2$; starting value versus final value: $p = 0.0163$), the $pO_2$-values showed after the tenth Iopromide injection over 110 seconds a tendency to decrease and then to remain up to 200 seconds on a lower level without an increase of $pO_2$-values again.

Looking at the time courses of $pO_2$-values of both groups from a statistical view, they did not differ ($p = 0.135$).

The time courses averaged over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups before, after the first, the fifth and the tenth bolus of both CMs are shown in Figure 5.

While the mean $pO_2$-value had only decreased by 0.3 mmHg from 29.9 ± 4.3 mmHg to 29.6 ± 4.3 mmHg ($p = 0.8799$) after the tenth Iodixanol bolus, it decreased by 5.9 mmHg from 34.0 ± 4.3 mmHg to 28.1 ± 4.3 mmHg after the tenth Iopromide bolus ($p = 0.044$). This revealed a remarkable difference in the influence of these CM on the oxygen partial pressure in the kidney.

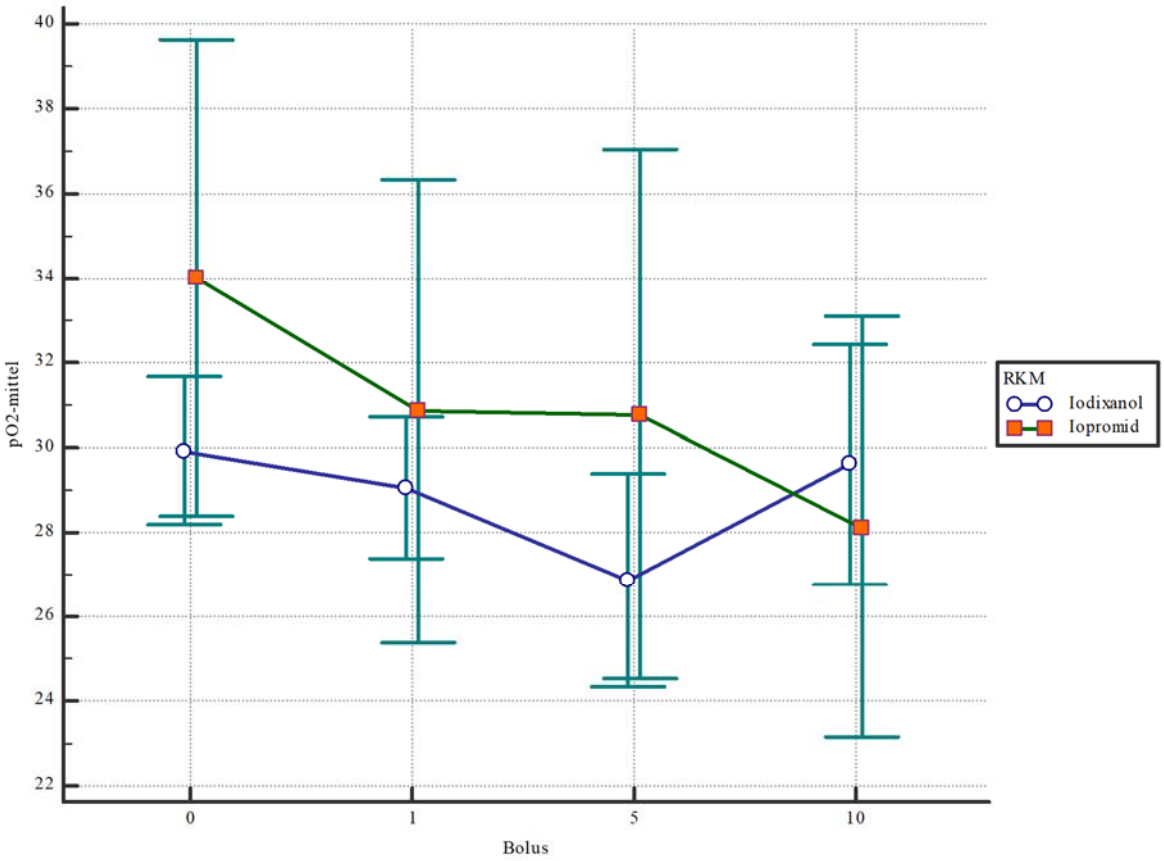


**Fig. 5**: Time courses averaged over 200 seconds of mean $pO_2$-values in the outer renal medulla of both animal groups before, after the first, the fifth and the tenth bolus of Iodixanol or Iopromide

## 4. Discussion

The study revealed differing effects of two iodinated contrast media on the oxygen partial pressure in the cortico-medullar region. While after the injection of Iopromide a continuous decrease of the $pO_2$ occurred, the $pO_2$ also decreased but then returned to baseline values after the injection of Iodixanol (see Figure 5).

Baseline tissue oxygen partial pressures in the outer medulla found in this study are comparable to those in previous studies. Liss et al. described $pO_2$-values between 30±3 mmHg and 36±3 mmHg in the outer medulla of rats and Baumgärtel found in dogs that almost 50% of all cortical $pO_2$ values were in the range between 24 – 40 mmHg [17, 27]. Through the randomized assignment of animals to one of the two CM-groups there were two animals in the Iopromide group which had $pO_2$ values clearly above the mean $pO_2$ values, and one animal with markedly lower $pO_2$ values. However, all of the measured baseline values were within the reference range of renal $pO_2$ values. This explains the slightly and non-significant different $pO_2$ levels of the two groups at baseline and especially why the standard deviations differed between the two groups.

The heart rate remained constant during the examination period and did not differ between both groups. Both, the systolic and the diastolic blood pressures increased by

about 19%, which might have been induced by the medication [20, 28-31]. The mean blood pressures and the intraoperative courses of blood pressure, however, were comparable for both groups. That allows to neglect potential differences in systemic hemodynamic influences of the two iodinated contrast-media on the kidney perfusion. Body temperature was measured rectally and showed 37.7°C in both groups, so that differences in temperature could also be excluded as reason for the differing development of tissue $pO_2$. All animals of both groups peri-operatively received 500 ml NaCl solution (0.9%) leading to a dilution of the circulating blood volume for a short period of time, which was shown to be accompanied by a slight amelioration of the capillary perfusion [32].

CM were reported to cause disorders of the microcirculation in kidneys of rats and mice [9, 17, 18, 26]. However, in the unilobar kidneys of these animals the urine is clearly more concentrated, and the anatomical conditions do not allow the comparison of results observed in these animals with those from pigs or humans [33, 34]. In addition, Liss injected much higher volumes of CM (1600 mg I/kg bw). Moreover, the CM were not warmed up to 37 °C but injected at room temperature, which might contribute to the markedly stronger $pO_2$-decrease by 40% from 30±3 mmHg to 18±4 mmHg, compared to our study [17].

The strong and for some time persisting $pO_2$-decrease in the cortico-medullar region after repeated injections of Iopromide is thought to be a consequence of a reduction in the renal blood flow, which was described to follow the injection of Iopromide in the suprarenal aorta in renal arteries as well as in cortical capillaries [20]. This decrease in perfusion is combined with a reduction in the convective oxygen transport in the microcirculation, which in combination with the lowered oxygen release from erythrocytes, the rigidification of echinocytically transformed erythrocytes, and the buckling of endothelial cells can cause such a decline in the oxygen partial pressure in the renal tissues [10-13, 16, 35, 36]. Not only in the kidneys, but also in other body organs alterations of the microcirculation were found, depending on the type of CM applied. The CM Iopromide, which exerted the strongest effects on cells *in vitro*, induced in down-stream skin capillaries of patients with coronary artery disease a massive deterioration of the cutaneous microcirculation after the injection into the afferent artery [32]. Even an arrest of capillary blood-flow up to three minutes occurred [32]. In a large animal model Iopromide, but not Iodixanol, induced a decrease of the myocardial oxygen partial pressure after injection into the left coronary artery [37, 38]. Very recently, Calzavacca reported that the repeated intra-arterial administration of Iodixanol did not lead to a reduction of the blood flow in another species of large mammals (ewes) [21].

The results of this study are also in line with former clinical studies. Möckel et al. found that the decline in renal blood flow velocity was more pronounced in patients receiving

Iopromide (from 41.6 cm/s to 29.3 cm/s) than in those receiving Iodixanol (from 19.3 to 17.8 cm/s; $p = 0.008$ for the difference of relative decline) [22]. In addition, Treitl et al. showed in patients with normal renal function that repeated injections of Iodixanol did not induce an increase in the Renal Resistive Index [23].

The outer cortical region has a high metabolic activity, so that a decrease of the $pO_2$ might be injurious. A $pO_2$ decrease in the outer medulla was described to induce mitochondrial swelling to nuclear pyknosis and cell death in correlation to ischemia, the more severe the ischemia was the more pronounced was the injury [39-41].

Repeated application of iodinated contrast media can have a significant influence on the oxygen partial pressure ($pO_2$) in the renal cortico-medullar region of large animals. Depending on the type of the CM applied the decrease of $pO_2$ coincides with a redistribution of blood away from the cortex. The biggest impact of repeated CM injections did not appear up to the fifth injection but up to the $10^{th}$ injection. The study revealed that Iodixanol – in contrast to Iopromide - induced no changes of the mean oxygen partial pressure in the cortico-medullar region, which confirms that this iodinated contrast medium on its way through the medullar capillaries did not hinder the flow of blood through the renal micro-vessels in a large animal model with a renal morphology and function comparable to human kidneys.

Coinciding with a hypothesis from Brezis such a microcirculatory disorder might be the basis for the development of CI-AKI.

## Ethical approval

The Bavarian Institutional Animal Care and Use Committee approved the study protocol for the experiments performed in this study (number: 54-2532.1-31/13). All procedures were carried out in accordance to the EU Directive 2010/63/EU for animal experiments. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

## Financial disclosure

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