Acute renal haemodynamic effects of radiocontrast media in patients undergoing left ventricular and coronary angiography

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Abstract

Background. Tubular toxicity and renal ischaemia have been implicated in the pathogenesis of radiocontrast media induced nephropathy (CIN), but their respective role remains unclear.

Aims. In order to evaluate changes in renal blood flow in response to intra-arterial contrast media administration, we aimed to continuously measure renal arterial perfusion by means of renal blood flow velocity (RBFV) during left ventricular and coronary angiography and subsequent coronary intervention in patients with chronic kidney disease (CKD).

Patients and Methods. Ten patients (7 males, 63.4 ± 11.7 years) with serum creatinine (SCr) >1.5 mg/dl participated in the study. The first five patients received low-osmolar iopromide and the others iso-osmolar iodixanol contrast medium. RBFV was measured using a 0.014-inch Doppler guide wire, which was inserted through a separate contralateral femoral sheath via a 5 F Cobra diagnostic catheter into the renal artery. Data were recorded at 500 Hz to allow beat-to-beat analysis of RBFV and pressure. All patients were pre-treated with acetylcysteine and hydration.

Results. Immediately after left ventricular angiography no significant changes in RBFV were detected. Over time, however, following repeated administration of the additional contrast medium into the coronary arteries, RBFV decreased significantly from baseline until the end of the investigation, 28.4 (19.1/42.7) to 22.9 (16.9/30.6) cm/s (median and quartiles; P = 0.005), in the absence of significant changes in systemic arterial blood pressure. In individual patients the reduction in RBFV varied from 3.7% to 39.5%.

Conclusions. The administration of non-ionic low-osmolar contrast media has no immediate effect on renal perfusion in patients with CKD. However, during the course of coronary angiography a gradual decline in renal blood flow may occur, the extent of which varies, presumably depending on individual pre-disposition as well as on the amount of the contrast medium.

Keywords: acute renal failure; coronary angiography; iodoxanol; iopromide; renal artery blood flow velocity

Introduction

Radiographic diagnostic and therapeutic procedures are increasingly being used worldwide and this has resulted in an increasing incidence of contrast media-induced nephropathy (CIN) [1,2]. CIN is usually defined as an increase in serum creatinine (SCr) concentration of >25% above baseline or >0.5 mg/dl within 48 h after radiocontrast media (RCM) administration [3–6]. The occurrence of CIN is variable and usually low in the general population. Depending on the presence of certain risk factors, the incidence of CIN increases, but the rates reported from different centres vary significantly [7]. In patients with pre-existing kidney disease who undergo contrast studies, CIN occurs in up to 42% of cases. The development of CIN is associated with a significant increase in both in-hospital and 1-year mortality, especially if haemodialysis treatment is required [2].

Extensive research has been dedicated to identifying risk factors for a decline in renal function after RCM application. Pre-existing chronic kidney disease (CKD), the presence of congestive heart failure, diabetes mellitus and RCM cumulative dose were shown to be the most important and independent risk factors [8–11]. In patients who undergo
coronary angiography and/or intervention, one or more of these risk factors are quite often found [11].

The impairment of renal function after RCM exposure is multi-factorial. Mainly two pathophysiological mechanisms have been proposed: (1) RCM-induced direct cytotoxic effects and (2) RCM-induced vasoconstriction followed by either regional hypoxic damage or ischaemia/reperfusion injury [12]. In an early landmark experimental study in dogs, Katzberg et al. showed a biphasic response to intra-arterial renal RCM administration; a short period of hyperperfusion, then vasoconstriction with hypoperfusion and restoration of normal flow within several minutes [13]. The hypoperfusion was more pronounced with higher osmolarity of the contrast medium. In line with these observations, in a rat model of CIN, which includes the inhibition of nitric oxide and prostaglandin synthesis in addition to RCM administration, severe tissue hypoxia was demonstrated in the outer renal medulla [14–16].

Human studies, in which renal blood flow (RBF) was measured using a left renal vein thermodilution catheter, could not confirm a fall in RBF after bolus injection of the contrast medium, although a biphasic pattern of RBF was occasionally observed within a longer time frame (hours) [17,18]. One of the limitations of this technique is that thermodilution lacks sufficient temporal resolution to detect changes in blood flow that may occur within minutes [13].

In order to increase the understanding of renal haemodynamic changes in patients at risks for CIN who receive RCM during coronary interventions, we were interested in monitoring RBF at high resolution during the entire coronary procedure, including ventricular and coronary angiography. We therefore used Doppler guide wires in 10 patients with CKD to measure renal artery blood flow velocity, which is a reliable method to determine changes in RBF, as we have previously shown in an experimental model [19].

Patients and methods

Patients

Ten patients (7 male, 63.4 ± 11.7 years) with SCr > 1.5 mg/dl were included in the study. All patients underwent coronary and left ventricular angiography for clinical reasons and in accordance with current guidelines.

The study protocol was approved by the Ethics Commission of the Charité (authorization code 171/2002). Patients signed written informed consent the day before the procedure.

Renal blood flow velocity measurements

The method of measuring RBF by means of Doppler determination of RBF velocity (RBFV) is based on the assumption that the renal artery trunk has a constant diameter. The method has previously been validated by our group in pigs using simultaneous measurements of RBF and RBFV [19]. Normal values of RBFV have recently been obtained in humans [20]. RBFV was measured using a 0.014-inch Doppler guide wire, which was inserted through a separate contralateral femoral sheath via a 5 F Cobra diagnostic catheter into the renal artery. The positioning of the catheters was only guided by the topographic anatomy and typical flow patterns. Data were recorded at high resolution (500 Hz) to allow beat-to-beat analysis of RBFV and pressure.

Protocol

All patients received pre-treatment with ACC and hydration according to current recommendations; 600 mg acetylcysteine (ACC) twice daily p.o. were given the day before and after the procedure and hydration with 1 ml/kg isotonic saline i.v. was performed between 12 h prior and 12 h after the procedure [21]. Patients underwent instrumentation with a 5 F sheath inserted into the right femoral artery and a 7 F sheath inserted into the right femoral vein for routine coronary diagnostic procedure and routine right heart catheterization. A second 5 F sheath was introduced into the left femoral artery. Using the left sheath, a 0.0014-inch Doppler guide wire (Cardiometrics Flowire®, Cardiometrics, Mountain View, CA, USA) was inserted into the left main renal artery trunk by a 5 F Cobra diagnostic catheter. Renal artery pressure was continuously monitored using saline filled standard tubes. Femoral artery pressure was virtually identical to renal artery pressure and confirmed that the catheter inside the renal artery does not cause relevant occlusion.

After assessment of right heart pressures and cardiac output by thermodilution, the Swan-Ganz catheter was removed and a second 5 F Cobra catheter was introduced into the ipsilateral renal vein. Renal venous pressure was recorded continuously. Blood samples for the determination of RCM concentrations were taken from the arterial sheath and the renal venous catheter at baseline, immediately after LV angiography (LVA) and at the end of the procedure. Angiographic procedures were only started after complete instrumentation and assessment of baseline values; Figure 1 shows catheter positions on an x-ray image. Predefined steps for analysis of RBFV were: baseline, before and after LVA, after completion of the shortest investigation (approximately at 30 min; after completion of diagnostic angiography) and at the end of the investigations (two points in 2 min to confirm stability of RBFV).

The first five patients received low-osmolar iopromide and the other five iso-osmolar ioxanol RCM. For ventriculography 40 ml of the contrast medium was used. Creatinine was measured on the day before and 48 h after the intervention and the estimated glomerular filtration rate (eGFR) was calculated using the MDRD IV equation [22].

Measurement of RCM concentrations

RCM concentrations are reflected by plasma iodine concentrations. Serum samples of 1 ml were directly transferred to gamma counter tubes (Sarstedt, Nuremberg, Germany) and diluted with an equal volume of sterile water. Measurement of iodine content was performed using an X-ray fluorescent analyser (Kaufman, San Francisco, USA). For this purpose, iodine atoms are excited to fluorescence by a 33 keV γ-radiation of 241americium. The evaluation was performed with software Maestro II (version 1.40, EG &
Fig. 1. X-ray showing catheters in place. The right catheter is placed in the ostium of the renal artery and the Doppler guide wire is inserted into the main trunk of the renal artery. The left catheter lies in the corresponding renal vein.

Ortec). The iodine concentrations of the samples are presented as mg/ml.

Statistics
As normal distribution cannot be anticipated in a small sample size, central tendencies are described by the median and quartiles. For the comparison of (relative) RBFV values at distinct pre-defined timepoints, the non-parametric exact Wilcoxon test was used. The high-resolution flow values after radiocontrast bolus administration into the left ventricle are displayed as means and standard deviation (Figure 2). Statistical comparison of both contrast agents used were done at two predefined points in time: after 30 min (same time of examination for all patients) and at the end of the investigation, at which time elapsed was different between patients and groups.

Linear correlation analyses were done (Pearson). All calculations were performed using the SPSS® V 13.01 statistical package.

Results
Baseline characteristics
The baseline characteristics of all 10 patients are shown in Table 1. Baseline creatinine values after pre-treatment with ACC and hydration ranged from 1.3 to 3.7 mg/dl, corresponding to eGFR values of 13.67 to 58.7 ml/min × 1.73 m². There were no significant differences between the two groups of patients receiving either iso-osmolar or low-osmolar contrast medium in baseline creatinine [1.9 (1.5/2.9) mg/dl versus 1.7 (1.6/1.8) mg/dl, P > 0.2] or eGFR [39.1 (23.1/51.5) ml/min × 1.73 m² versus 45.5 (29.7/46.6) ml/min × 1.73 m², P > 0.2].

Five patients had diabetes, one in the group receiving iso-osmolar and four in the group receiving a low-osmolar contrast medium (see Table 1).

Duration of the procedure, amount of RCM and plasma iodine concentrations
Percutaneous coronary intervention was performed in all patients receiving iopromide and in two patients receiving iodixanol. Accordingly, the median duration of the procedure tended to be longer in the iopromide group [85 (32–150) min versus 38 (27–110) min], but the difference did not reach statistical significance (P > 0.2, Wilcoxon test). The amount of RCM administered was 310 (255/400) ml in the iopromide group versus 190 (125/305) (P = 0.151).

Iodine concentrations as an objective measure of contrast media load in all patients revealed significantly higher concentrations in arterial than in renal venous blood (data not shown). In patients receiving iodixanol, iodine concentrations at the end of the investigation tended to be lower than in patients receiving iopromide: 2.9 (2.6/7.4) versus 8.5 (4.6/9.9) mg/ml in arterial blood, (P = 0.095) and 2.4 (2.1/3.1) versus 4.7 (3.2/5.5) mg/ml in renal venous blood (P = 0.016). Individual values of iodine concentrations in renal venous blood at the end of the investigation are given in Table 1.

Changes in serum creatinine and eGFR
Mean values of SCr and eGFR did not change within 48 h after the intervention. Two patients showed an increase in SCr by >0.5 mg/dl (one in each group) but none required dialysis. Creatinine levels tended to be lower in the first five patients who received iopromide and increased more in the second five patients who received iodixanol (Table 1).

Baseline cardiac output and renal blood flow velocity
Baseline median cardiac output measured by thermodilution was 4.8 (3.5/6.5) l/min in patients receiving iodixanol and 3.8 (3.6/6.5) l/min (P > 0.2) in patients receiving iopromide. Angiographic left ventricular ejection fraction was 48.3% versus 28.8% (P > 0.2) respectively. Baseline values of RBFV ranged from 12.8 to 49.2 cm/s and were on average lower in the iodixanol group (19.3 versus 41.6 cm/s, P = 0.016).

Changes in renal haemodynamics
Immediately after left ventricular angiography, no significant changes of RBFV could be detected in any patient. Figure 2a shows a representative recording in a single patient; Figure 2b depicts the average RBFV in all 10 patients during the first 4 min after ventriculography. Pulsatility due to heartbeat and respiration is obvious in the individual recordings. Over time, with repeated administration of additional RCM into the coronary arteries, RBFV decreased significantly from baseline until the end of the
Renal perfusion during radiocontrast administration

Fig. 2. Renal blood flow velocity during the first 4 min after left ventricular angiography (injection at time point zero of the registration). The values were stable for at least 1 min prior to the injection. (a) Representative example of recording of blood pressure and renal blood flow velocity in a single patient (no. 10 in Table 1). (b) Mean and standard deviation of RBFV in all patients.

investigation from 28.4 (19.1/42.7) to 22.9 (16.9/30.6) cm/s ($P = 0.005$) (Figure 3). This decline is mainly due to a reduction in the patients receiving iopromide, who started from a significantly higher baseline (see above): 41.6 (28.5/47.7) at baseline versus 29.3 (20.7/38.0) cm/s at the end of the investigation, compared to 19.3 (15.7/26.8) at baseline versus 17.8 (14.1/24.3) cm/s at the end of the investigation in patients receiving iodixanol. The difference in the relative change in velocities reached statistical significance at the end of the investigation ($P = 0.008$). It must be pointed out that this was later in the iopromide group and after receipt of a higher contrast load (see above).

Correlation analysis (Pearson) of the individual contrast load (renal venous iodine concentration) and the relative change of RBFV from baseline showed a strong negative correlation ($r = -0.781, P = 0.008$) (Figure 4).

Discussion

The main findings of the present study are: (1) continuous monitoring of renal blood flow is feasible in patients using a Doppler flow wire, (2) using this technique in patients with CKD, there is no evidence for an immediate decline in renal perfusion after bolus injection of RCM into the left ventricle and (3) nevertheless, during the course of coronary
Fig. 3. Continuous monitoring of renal blood flow velocity during the whole procedure. Individual recording of one patient receiving iopromide.

Fig. 4. Correlation of renal venous iodine concentration as a measure of individual contrast load and relative change of RBFV from baseline in all 10 patients.
insertion of the flow wire into the renal artery was without any complications and was easily achievable in every patient. Although the technique is invasive, the small dimensions of the flow wire, with a diameter of ∼0.33 mm, allow it to be used during the course of interventions with minimal additive risk. In this trial we inserted the flow wire through an additional sheath inserted into the contralateral femoral artery, requiring additional arterial cannulation, in order to allow continuous recording. Given the observed stability of the recordings, discontinuous measurements following intermittent insertion into the sheath used for angiography appear to be an option that allows further risk reduction.

The range of baseline flow values was remarkable with a variation between 49.2 and 12.8 cm/s. Naturally RBFV depends on both RBF and the diameter of the renal artery. In a recent study on renal flow reserve, it was shown that the dimension of the renal artery does not change after the administration of vasodilator substances [20]. In this study we intentionally included patients with CKD, the type of contrast medium used and the pre-treatment with ACC and hydration. Despite a little change in RBFV in the early phase after RCM application, we did not observe a more gradual decline during the intervention period in the majority of patients. This decline resulted in an average decrease in RBFV of 15% and reached as much as 39.5% in individual patients.

When considering the possible underlying mechanisms of these reductions in renal arterial perfusion it appears noteworthy that these changes were observed at a constant mean arterial blood pressure of 98–100 mmHg, well within the range of the physiological autoregulation of renal perfusion and without significant changes over time (P > 0.2, Friedman test). Thus the observed decline in renal perfusion probably indicates an alteration of the normal autoregulatory mechanism and reflects renal vasoconstriction, provided that the cardiac output remained stable, which is usually the case during diagnostic angiography. However, since the cardiac output was not continuously monitored throughout the study, we cannot rule out that a systemic increase in vascular resistance occurred. With respect to the functional relevance, it is of note that animal experiments suggest that in particular the outer medulla experiences hypoperfusion in response to RCM administration [23]. Given that the outer medulla in normal kidneys already operates under conditions of limited oxygen availability, it is feasible that flow reductions of the magnitude observed in the present trial have the potential to induce distal tubular injury.

The reason for the delayed onset of renal hypoperfusion remains unclear. The amount of the contrast medium administered, and thus its plasma concentration, increased with time. In fact we found a strong correlation between iodine concentration and RBFV changes (Figure 4). The greatest amount of RCM at one time was given during the ventricular angiography, but a major reduction in RBFV was mainly seen at later stages of the investigation, mostly in patients who received high amounts of contrast dye (see Figure 4). It appears possible, therefore, that initially a vasoconstrictive stimulus is counterbalanced by compensatory mechanisms, which are then gradually overcome with increasing contrast load or lose efficacy with time. Conversely it is also

### Table 1. Characteristics of patients

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*iopromide, #iodixanol.
possible that the contrast medium filtered into the tubular space exerts direct toxic effects on tubular epithelial cells, as described in experimental studies [12,24], and that renal vasoconstriction occurs as a secondary response to tubular damage.

Apart from a marked interindividual variability in renal blood flow reduction the changes differed between patients receiving different contrast media. The decline in RBFV was much more marked in patients receiving iopromide as compared to iodixanol. A significant limitation in this respect is that the assignment of the two different contrast agents was not randomized in this pilot study. In fact there were significant differences between the two groups of five patients receiving either iopromide or iodixanol, including differences in baseline RBFV, the duration of the intervention and the total amount of RCM applied, which could be responsible for the different degrees of flow reduction. In contrast to the work by Aspelin et al. [25] recent data question that iso-osmolar contrast is superior to low-osmolar agents [26–28]. We believe that the methodology reported here offers a novel opportunity to systematically test potential differences between different contrast agents and will also allow these observations to be easily extended to patients with different degrees of renal insufficiency.

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Conflict of interest statement. None declared.

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