A primer in radiocontrast-induced nephropathy

Bernhard K. Krämer, Martin Kammerl, Frank Schweda and Matthias Schreiber

Klinik und Poliklinik für Innere Medizin II, Klinikum der Universität Regensburg, Regensburg, Germany

Despite recent medical progress in supportive medical therapy, the frequency of hospital-acquired acute renal failure has increased in recent years from \( \sim 5\% \) to \( 6.4\% \) [1,2]. Even more distressing is the fact that mortality associated with acute renal failure has remained high, i.e. on average \( \sim 60\% \) in more recent reports [1–11]. Radiocontrast-induced nephropathy (RCIN) is the third most common cause of hospital-acquired acute renal failure. When RCIN is defined as an increase in serum creatinine level of at least 25\% to at least 2 mg/dl within 2 days, most disturbingly RCIN continues to be associated with death by an odds ratio of 5.5 even when adjustments are made for comorbid factors, e.g. age, liver disease and physiological severity score [10]. It appears that renal failure increases the risk of death from pre-existing nonrenal conditions, but also that major nonrenal morbidity will develop in patients with RCIN [10]. RCIN not only reduces survival, but is also costly. In a recent clinical trial, the mean cost of treating adverse reactions to contrast media, which occurred in 193 patients, was €459 [12]. The mean cost of treating adverse reactions increased to €2064 in patients with a history of renal failure, i.e. serum creatinine >1.2 mg/dl. Among the 12 patients with adverse reactions causing excessive cost, 75\% had either pre-existing renal failure or developed RCIN [12]. The mean cost of treating RCIN was €1950, which is probably even an underestimate [12].

Incidence of radiocontrast-induced nephropathy

The proportion of hospital-acquired acute renal failure accounted for by RCIN has increased from 5\% in 1977 to 32\% in 1987 [6,13], but exact figures are difficult to obtain, since the definitions used by different researchers are not uniform. In the multicentre Iohexol Cooperative Study, 1196 patients were randomized to receive either the nonionic contrast agent iohexol (I) or the ionic agent meglumine/sodium diatrizoate (D) for cardiac angiography [14]. Patients were stratified into four groups: (i) renal insufficiency (RI; serum creatinine \( \geq 1.5 \text{mg/dl} \)) and diabetes mellitus (DM) both absent (n = 364); (ii) RI absent, DM present (n = 318); (iii) RI present, DM absent (n = 298); (iv) both RI and DM present (n = 216) [14]. The frequency of RCIN, defined as an increase of serum creatinine \( \geq 0.5 \text{mg/dl} \), was 8.5\% for iohexol (I) and 8.2\% for diatrizoate (D) in group i, 7.2\% (I) and 11.1\% (D) in group ii, 12.2\% (I) and 27.0\% (D) in group iii, and finally 33.3\% (I) and 47.7\% (D) in group iv. Obviously the risk of RCIN is increased considerably in patients with pre-existing renal failure, particularly when diabetes mellitus is present. When the clinically more relevant criterion of an increase of serum creatinine of \( \geq 1.0 \text{mg/dl} \) was used, the frequency of RCIN in group i was 0\%, in group ii <1\% each for I and D, in group iii 4\% (I) and 7% (D), and finally in group iv 12\% (I) and 27\% (D) [14]; possibly suggesting that nonionic (low osmolar) contrast-media are beneficial in patients with pre-existing renal failure, especially in diabetic patients. Davidson and colleagues [15] examined 1144 patients undergoing cardiac catheterization and found a low risk of RCIN (A S-creatinine \( \geq 0.5 \text{mg/dl} \)) in patients with normal renal function. When baseline S-creatinine concentration was >1.2 mg/dl, however, the risk of RCIN was higher and increased exponentially with S-creatinine concentration (i.e. 20\% RCIN when baseline S-creatinine was 2.0 mg/dl). Even irreversible renal failure may develop when radiocontrast media are administered to patients with advanced diabetic nephropathy and renal failure [16,17]. After intravenous pyelography RCIN was seen in 93\% of diabetic patients with baseline S-creatinine concentrations >5 mg/dl, and in 56\% it was irreversible [16]. Similarly, after coronary angiography 50\% of patients with diabetic nephropathy (S-creatinine concentration 5.9 mg/dl) developed RCIN, and in 21\% dialysis treatment was required within 14 days, although the median volume of nonionic contrast medium was only 30 ml [17].

Available modalities for prevention and treatment of radiocontrast-induced nephropathy

Hydration

In 1981 Eisenberg et al. [18] studied 537 patients undergoing cerebral, abdominal or peripheral angiography with relatively large volumes of radiocontrast. They received 550 ml of normal saline and 250 ml of...
heparinized saline per h during the procedure. RCIN could be avoided by this hydration protocol and this was later recommended for any type of angiography [19]. Brown et al. [20] studied retrospectively 518 patients with a baseline S-creatinine concentration of >1.9 mg/dl who were undergoing cardiac angiography. The 76 patients who developed RCIN had received a larger volume of radiocontrast, had lower diastolic blood pressure before angiography and had less hydration before angiography than 82 matched controls. The frequency of RCIN was lower in studies using a hydration protocol compared with studies without mandatory hydration [15,21]. This evidence for the benefit from hydration before radiocontrast cannot be taken as rigorous scientific proof, however, since this problem was never addressed in a controlled, randomized trial with sufficient statistical power.

**Diuretics**

There is no convincing proof for benefit from routine administration of furosemide or mannitol before or during angiography [21–23]. Furosemide may even adversely affect renal functional prognosis. There is some uncontrolled clinical evidence that temporary interruption of administration of diuretics or angiotensin-converting enzyme (ACE) inhibitors before radiocontrast administration may be beneficial.

**Calcium-channel blockers**

Encouraging results have been reported for the prophylactic use of calcium-channel blockers, but this treatment has not gained wide acceptance [24,25]. In a randomized, double-blind trial Neumayer et al. [24] examined the effect of nitrendipine administered 24 h prior to administration of radiocontrast to patients with normal renal function. The authors found that glomerular filtration rate (GFR) remained unchanged with pretreatment in contrast to a 26% decrease in GFR in the control group. These results were confirmed by another study with a short-term follow-up of only 2 h [25].

**Nonionic radiocontrast medium**

There has been considerable debate as to whether the type of contrast medium, i.e. ionic vs nonionic, low-osmolar vs high osmolar, influences the frequency of RCIN. It has been suggested that low-osmolar radiocontrast media cause less RCIN in patients with underlying renal failure with or without diabetes mellitus [14; reviewed in 26,27]. In a meta-analysis of 25 studies, Barrett and Carlisle [26] found an odds ratio for RCIN (increase in S-creatinine concentration of more than 0.5 mg/dl) of 0.5 (CI 0.36–0.68) for patients with pre-existing renal failure (S-creatinine concentration >120 µmol/l or creatinine clearance <70 ml/min). It was 0.75 (CI 0.52–1.1, n.s.) in patients with normal renal function. Barrett and Carlisle estimated that eight patients with pre-existing renal failure would have to be treated with low-osmolarity contrast media to prevent one case of RCIN [26].

**Preventive haemodialysis**

Removal of radiocontrast media in patients with pre-existing renal failure by haemodialysis does not prevent RCIN [28,29].

**Experimental strategies for prevention or treatment of radiocontrast-medium-induced nephropathy**

Promising experimental approaches for the prevention or treatment of RCIN comprise administration of atrial natriuretic peptide, endothelin-receptor blockers and prostaglandins [30–33]. These compounds are currently being studied in phase II/III clinical trials.

**Atrial natriuretic peptide**

Atrial natriuretic peptide (ANP) increases GFR and glomerular hydrostatic pressure by dilating afferent arterioles while constricting efferent arterioles [34]. Furthermore, ANP blocks tubular reabsorption of sodium, causes the redistribution of renal medullary blood flow, reverses endothelin-induced vasoconstriction and disrupts the tubuloglomerular feedback [34]. These properties made ANP an attractive candidate for prevention and treatment [32]. Subsequently, ANP was shown to prevent ischaemic and toxic acute renal failure [35–37], as well as RCIN in rats and dogs [38,39]. In a dog model of heart failure, induced by rapid ventricular pacing, the prolonged, radiocontrast-induced decrease in GFR could be blocked by ANP [38].

**Endothelin receptor blockers**

The endothelins are a family (ET-1, ET-2, ET-3) of peptides which are potent vasoconstrictors, preferentially in the renal vascular bed, causing intense constriction of both vas afferens and vas efferens. They also counteract some of the actions of nitrous oxide (NO) and prostaglandins. They cause natriuresis at low doses and sodium retention at higher doses [40,41]. A role of endothelins in RCIN is supported by the observation of endothelin release from endothelial cells after radiocontrast in vitro and in vivo [42,43]. Blockade of endothelin ET₁ and ET₂ receptors prevents RCIN either partially or completely [44–46].

**Prostaglandins**

The vasodilatory eicosanoids prostaglandin PGE₂ and PG₁₂ (prostacyclin) counteract vasoconstrictive actions of endothelins [44,47]. They dilate the afferent arterioles; and have cytoprotective effects on tubular epithelium [44,47,48]. Most animal models of RCIN use blockade of cyclo-oxygenases, e.g. by indomethacin. This observation illustrates the importance of an intact
RCIN was defined as an increase of S-creatinine concentration of \( \geq 0.5 \text{ mg/dl} \) or \( \geq 25\% \) after 24 or 48 h in patients with pre-existing renal failure receiving placebo (PLA), 0.01 µg/kg/min of anaritide (ANA), 0.05 µg/kg/min of anaritide, and 0.1 µg/kg/min of anaritide. Information on important confounding variables [mean baseline S-creatinine (Scr), % of diabetics, volume, and type of contrast medium] is also given.

### Table 1. Effect of anaritide on frequency of radiocontrast-induced nephropathy (RCIN)

<table>
<thead>
<tr>
<th></th>
<th>PLA</th>
<th>0.01 ANA</th>
<th>0.05 ANA</th>
<th>0.1 ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scr, %</td>
<td>2.1</td>
<td>2.0</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>RCIN (overall, %)</td>
<td>19</td>
<td>23</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>RCIN (diabetics, %)</td>
<td>26</td>
<td>33</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>RCIN (nondiabetics, %)</td>
<td>9</td>
<td>13</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>% Diabetics</td>
<td>60</td>
<td>51</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
<td>132</td>
<td>162</td>
<td>141</td>
<td>148</td>
</tr>
<tr>
<td>Ionic/high osmolar (%)</td>
<td>44</td>
<td>44</td>
<td>53</td>
<td>48</td>
</tr>
</tbody>
</table>

### Table 2. Effect of an endothelin receptor antagonist on the frequency of radiocontrast-induced nephropathy (RCIN)

<table>
<thead>
<tr>
<th></th>
<th>PLA</th>
<th>SB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scr</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>RCIN (( \geq 0.5/25% ) Scr increase at 48h)</td>
<td>29</td>
<td>56*</td>
</tr>
<tr>
<td>ASCr at 48h post radiocontrast</td>
<td>0.35</td>
<td>0.72*</td>
</tr>
<tr>
<td>% Diabetics</td>
<td>58</td>
<td>69</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
<td>122</td>
<td>104</td>
</tr>
</tbody>
</table>

*Significant difference.

Study in patients with pre-existing renal failure receiving placebo (PLA) or the nonselective endothelin receptor antagonist SB209670 (SB). Information on important confounding variables (mean baseline serum creatinine, % of diabetics, volume, and type of contrast medium) is also given.

prostaglandin system for handling of contrast media by the kidney [49,50].

### Testing these strategies in clinical trials

#### Atrial natriuretic peptide

The results of the trial of the Auriculin Anaritide Acute Renal Failure Study Group had been promising. This was a multicentre, randomized, double-blind, placebo-controlled trial of anaritide (25-amino-acid synthetic form of atrial natriuretic peptide) and involved 504 critically ill patients with acute tubular necrosis [51]. Subgroup analysis had suggested that anaritide improves dialysis-free survival in oliguric patients. Nevertheless the subsequent definite trial to study anaritide in oliguric patients with acute renal failure did not confirm this result [52]. Anaritide has also been studied prospectively as an agent to prevent RCIN. Kurnik et al. [53] studied 247 patients at risk of RCIN, i.e. with a baseline S-creatinine concentration \( >1.5 \text{ mg/l} \), and diabetes mellitus in 50% of patients. Three doses of anaritide or placebo were administered intravenously for 30 min before and for 30 min after the angiographic procedure (for a maximum of 3 h). The frequency of RCIN in the placebo group was 19%, in the 0.01 µg/kg/min anaritide group 23%, in the 0.05 µg/kg/min anaritide group 23% and in the 0.1 µg/kg/min anaritide group 25%. No treatment benefit was found in subgroup analysis in diabetic patients (Table 1) [53].

#### Endothelin receptor blockers

Based on experimental data endothelin receptor blockers appeared promising for preventing RCIN. In a multicentre, double-blind, randomized, placebo-controlled trial, intravenous pretreatment with the nonselective endothelin receptor antagonist SB209670 was studied in 158 patients with renal failure undergoing coronary angiography [54]. The frequency of RCIN was even higher in the endothelin receptor antagonist than the placebo group (Table 2). Radiocontrast dose and proportion of diabetic patients were comparable in both groups. All patients were hydrated before administration of radiocontrast (1 ml/kg/h 0.45% saline for at least 8 h). A beneficial effect of selective endothelin ETA receptor antagonists on RCIN is not excluded, however, by the disappointing outcome of this first study.

#### Prostaglandin PGE$_1$

A pilot study comprised 117 patients with pre-existing renal failure (serum creatinine concentration \( >1.5 \text{ mg/dl} \); 52% diabetic patients). Three different doses of PGE$_1$ (10, 20 or 40 ng/kg/min) and placebo were administered intravenously starting 1 h \( \pm 30 \text{ min} \)

### Table 3. Effect of prostaglandin PGE$_1$ on the frequency of radiocontrast-induced nephropathy (RCIN)

<table>
<thead>
<tr>
<th></th>
<th>PLA</th>
<th>10 PGE$_1$</th>
<th>20 PGE$_1$</th>
<th>40 PGE$_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SCR</td>
<td>2.4</td>
<td>2.3</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>RCIN (( \geq 0.5 \text{ increase in SCR} ))</td>
<td>52</td>
<td>31</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>RCIN (( \geq 1.0 \text{ increase in SCR} ))</td>
<td>24</td>
<td>6</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
<td>165</td>
<td>159</td>
<td>154</td>
<td>168</td>
</tr>
<tr>
<td>Nonionic contrast medium (%)</td>
<td>86</td>
<td>91</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>% Hypotension</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>35</td>
</tr>
</tbody>
</table>

Patients with pre-existing renal failure received placebo (PLA), 10 ng/kg/min of prostaglandin PGE$_1$, 20 ng/kg/min of prostaglandin PGE$_1$, and 40 ng/kg/min of prostaglandin PGE$_1$. Information on important confounding variables (mean baseline serum creatinine, volume and type of contrast medium) is also given.
before angiography and lasting for 6 h. The study was double-blind and randomized [55]. The investigators were encouraged to hydrate their patients before angiography, but a mandatory hydration protocol was not used. The frequency of RCIN was markedly lower in patients receiving PGE₁, despite similar baseline serum creatinine concentrations, contrast medium volumes and types (Table 3). At the highest dose of this dose-finding study, hypotension was more frequent. It is possible that the higher frequency of hypotension caused a trend for RCIN to be more frequent at the highest PGE₁ dose. The encouraging results of this study have to be confirmed, however, by a definitive study with a sufficient number of patients.

The magnitude of the problem

The number of patients at risk for RCIN is high. In the US in 1995 an estimated 1.2 million diagnostic cardiac catheterizations and 420,000 coronary angioplasties were performed; corresponding numbers in Germany in 1997 were 487,000 diagnostic cardiac catheterizations and 138,000 coronary angioplasties. The percentage of patients at special risk for RCIN, i.e. with pre-existing renal failure (≥1.5 mg/dl S-creatinine), lies somewhere between 3.5 and 15.5%. The former estimate is based on a sample of 2,846 sequential cardiac catheterizations at the Department of Internal Medicine, University of Regensburg: the latter is based on a sample of 1,184 sequential interventional cardiac catheterizations at the John Hopkins Hospital, Baltimore (A. Whelton MD, personal communication). When conservative estimates are used (5% of patients with pre-existing renal failure, risk of RCIN of 20%) 16,200 patients per year will suffer from RCIN in the US, and 6,250 patients in Germany. When one takes into account the cost of treatment resulting from: (i) intermittent or chronic dialysis treatment, (ii) prolonged hospital stay, (iii) delayed surgical or interventional procedure, (iv) intensive ambulatory follow-up, it becomes obvious that more widespread use of prophylactic measures of proven benefit, e.g. hydration, and the development of new therapeutic approaches, e.g. pharmaceutical intervention, are a matter of high priority.

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References

26. Barrett BJ, Carlosli EJ. Metaanalysis of the relative toxicity of

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