The Pathogenesis and Prevention of Radiocontrast Medium-Induced Renal Dysfunction

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Introduction

With the advent of radiocontrast media (RCM), diagnostic radiology advanced tremendously. However, despite ongoing refinement of these agents, the risk of contrast-induced acute kidney injury (CI-AKI) remains. Although risk factors for CI-AKI have been elucidated, there have been few advances in prevention or treatment other than adequate prehydration and continued hydration after administration. In early reports, it was found that the third most common cause of hospital-acquired acute kidney injury (AKI) resulted from use of RCM for imaging studies, accounting for 11% of AKI cases (Nash et al., 2002; Shusterman et al., 1987). In more recent analyses, this has become less common (Quader et al., 1998); however, it is not yet a rare occurrence, with general incidence rates decreasing from 15% to 20% to approximately 7% (Bartholomew et al., 2004). In spite of the current availability and use of low-osmolar RCM, AKI continues to be observed in the hospital setting following radiographic studies (Lasser et al., 1997; Quader et al., 1998; Shusterman et al., 1987; Weisbord et al., 2008a,b), and there are an ever increasing number of radioimaging studies being performed in critically ill patients.

Since the 1960s, investigators have used various animal models to define the mechanisms that contribute to the development of RCM-induced renal dysfunction. Clinical studies have also attempted to outline and prevent this problem. This chapter presents an overview of the history, epidemiology, and pathophysiology of renal dysfunction following RCM administration. Preventive strategies derived from clinical studies are also discussed.

History

Radiocontrast agents were first used for in vivo angiographic studies in the early 1920s (Osborne et al., 1923). Agents used during this period include strontium bromide, thorium dioxide, and sodium bromide. These agents were associated with an increased incidence of malignancies and prolonged radioactivity (Osborne et al., 1923; Silpananta et al., 1983). Organic diiodinated preparations were also used during the early 1920s (Sutton, 1987), and the first case report of renal dysfunction following their use was announced in 1931 (Pendergrass et al., 1942). Subsequently, these compounds were replaced in the mid-1950s with triiodinated compounds.

The presence of three atoms of iodine per molecule, as opposed to one or two, provided an ideal imaging substance. These new compounds were found to be less toxic, but more viscous, than the diiodinated. The triiodinated RCM also lacked water solubility secondary to the high-osmotic composition. The hyperosmolarity induced in serum following the administration of these compounds is thought to be a primary cause of acute decline in renal function (Alexander et al., 1978; Ansari and Baldwin, 1976; Barrett and Carlisle, 1993; Bartley et al., 1969; Byrd and Sherman, 1979; Diaz-Buxo et al., 1975; Krumlovsky et al., 1978).

Investigators in the early 1970s then developed the nonionic, monomeric RCM. These newer RCM had lower osmolality effects on serum than the older ones, although the osmolality of these agents is still double that of blood. There was an expectation, however, that the reduction in osmolality would result in reduced nephrotoxicity (Spataro, 1984). These newer agents are termed nonionic because an organic side chain has replaced the carboxyl group, and hence they do not ionize in solution. They also differ from the ionic RCM in the number of osmotic particles per iodine atom (roughly 50% less than ionic agents), which accounts for the low osmolar (Alexander et al., 1978; Ansari and Baldwin, 1976; Barrett and Carlisle, 1993; Bartley et al., 1969; Byrd and Sherman, 1979; Diaz-Buxo et al., 1975; Krumlovsky et al., 1978; Pendergrass et al., 1942; Spataro, 1984; Sutton, 1987). In the 1980s, nonionic dimers were introduced (two nonionic triiodinated benzoic rings were attached), which have an osmolality similar to that of blood (iso-osmolar agents) (Morcos and Thomsen, 2001).

Since the mid-1980s, attempts to develop nontoxic RCM have led to the development of gadolinium-diethyltriamine pentaacetic acid (Gd-DTPA) and carbon dioxide (Seeger et al., 1993; Spinosa et al., 1999). Eventually, in the 1990s iso-osmolar nonionic ioxanol with the same physiologic osmolality as blood was developed; since then variants of ioxanol have been developed with different physical properties. The historic evolution of RCM is summarized in Table 1.
Pharmacology and Physiology

RCMs are organized into two groups: ionic and nonionic. The major difference between these groups is their divergent osmolalities, not their iodine content or viscosity. Because the renal toxicity of an agent is more closely linked to its osmolality than to its ionic characteristics, lower osmolar agents are preferred (Benness, 1970; Bettmann, 1982; Burgener and Hamlin, 1981; Dean et al., 1978; Gaspari et al., 1997; Haustein et al., 1992; Morris and Fischer, 1986; Mudge, 1980, 1990; Rocco et al., 1996; Sage, 1983; Schiantarelli et al., 1973; Spataro et al., 1982; Talner, 1972; Ueda et al., 1998).

The RCM of each group that are used in medical practice are derivatives of 2,4,6-triiodinated benzoic acid (Figure 1).

The most widely used class of hyperosmolar RCM is the diatrizoate derivatives, which are water soluble and have a low pK_a due to their carboxyl group (Bettmann, 1982; Mudge, 1990). They exist as anions in biological systems and are confined to the extracellular space (Mudge, 1990). They do not bind significantly to serum proteins and are almost entirely cleared by the kidneys (99%), with a small component accounted for by gastrointestinal and hepatic clearance pathways (1%). The extrarenal removal of the diazoate derivatives becomes more pronounced in renal failure (Schiantarelli et al., 1973; Talner, 1972) and can account for up to 25–36% of the administered dose (Ackrill et al., 1976; Cattell et al., 1967). Despite this, the mean half-life of RCM is roughly doubled in dialysis patients as compared to the mean half-life in persons with functional kidneys (Ackrill et al., 1976; Cattell et al., 1967; Milman and Christensen, 1974; Schindler et al., 2001; Waaler et al., 1990).

Two types of RCM, triiodinated compounds and DTPA, are freely filtered by the glomerulus and neither secreted nor reabsorbed by the tubules (Burgener and Hamlin, 1981; Haustein et al., 1992). Consequently, these agents are similar to inulin, a marker of glomerular filtration rate (GFR). In persons with normal renal function, the plasma half-life of RCM is between 30 and 60 min (Burgener and Hamlin, 1981; Morris and Fischer, 1986), and the peak time for excretion of RCM is about 3 min following intravenous injection. Peak urine iodine concentrations occur approximately 1 h after RCM administration (Mudge, 1980; Spataro et al., 1982; Ueda et al., 1998).

Although the initial concentration of RCM in the tubule is the same as that in the plasma, the urinary concentration of RCM increases five- to tenfold as a result of proximal tubular sodium and water reabsorption. With meglumine derivatives, this increase is partially attenuated due to higher urine flow rate. Increased concentration of RCM may explain, in part, enhanced toxicity to the loop of Henle portion of the renal tubule.

Proximal tubular sodium reabsorption following RCM treatment is independent of hydration and is influenced by diuretics and osmotic load (Cattell et al., 1967; Talner, 1972). It is conceivable, therefore, that the concentration of RCM in the ultrafiltrate

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**Table 1** The evolution of clinically used radiocontrast media

<table>
<thead>
<tr>
<th>Agents</th>
<th>Year used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium iodide</td>
<td>1918, 1923</td>
</tr>
<tr>
<td>Strontium bromide</td>
<td>1923</td>
</tr>
<tr>
<td>Thorium dioxide</td>
<td>1923</td>
</tr>
<tr>
<td>Monodiodinated compounds: lopax and others</td>
<td>1929</td>
</tr>
<tr>
<td>Diiodinated compounds: diodrast, skiodan, diodone, and others</td>
<td>Early 1930s</td>
</tr>
<tr>
<td>Triodinated compounds: sodium diatrizoate, diatrizoate meglumine, etc.</td>
<td>Mid-1950s</td>
</tr>
<tr>
<td>Low-osmolar (nonionic) compounds: metrizamide, iohexol, iopamidol, and others</td>
<td>Late 1970s, early 1980s</td>
</tr>
<tr>
<td>Iso-osmolar (nonionic) compounds: ioxilanl</td>
<td>1990s</td>
</tr>
</tbody>
</table>

*Initially suggested for use as a radiocontrast agent.

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**Table 2** Physical properties of example radiocontrast agents

<table>
<thead>
<tr>
<th>Ionic</th>
<th>Osmolality (mOsm l⁻¹)</th>
<th>Iodine (%)</th>
<th>Viscosity (37°C mPas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iothalamate meglumine (Conray 60)</td>
<td>1217</td>
<td>28</td>
<td>4.0</td>
</tr>
<tr>
<td>Sodium diatrizoate (Hypaque)</td>
<td>1470</td>
<td>30</td>
<td>2.5</td>
</tr>
<tr>
<td>Meglumine-sodium diatrizoate (Renograin 76)</td>
<td>1690</td>
<td>37</td>
<td>9.1</td>
</tr>
<tr>
<td>Iothalamate-sodium (Conray 400) onionic</td>
<td>1965</td>
<td>40</td>
<td>4.5</td>
</tr>
<tr>
<td>Iotrol</td>
<td>300</td>
<td>30</td>
<td>9.1</td>
</tr>
<tr>
<td>Metrizamide</td>
<td>450</td>
<td>28</td>
<td>5.0</td>
</tr>
<tr>
<td>Iopamidol +</td>
<td>570</td>
<td>28</td>
<td>3.8</td>
</tr>
<tr>
<td>Iohexol</td>
<td>620</td>
<td>28</td>
<td>4.8</td>
</tr>
<tr>
<td>Iodixanol (Visipaque) – (270 mgI ml⁻¹)</td>
<td>290</td>
<td>49</td>
<td>6.3</td>
</tr>
<tr>
<td>Iodixanol (Visipaque) – (320 mgI ml⁻¹)</td>
<td>290</td>
<td>49</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Terms in brackets are trade name.
The range of molecular weights for radiocontrast media mentioned above is 636 (diatrizoate) to 1626 (Iotrol).
leaving the proximal tubule may be up to 50 or 100 times that entering the tubule (Benness, 1970; Burgener and Hamlin, 1981; Cattell et al., 1967; Dean et al., 1978; Morris and Fischer, 1986; Mudge, 1980; Sage, 1983; Spataro et al., 1982; Talner, 1972; Ueda et al., 1998). Furthermore, in states of dehydration, the concentration of RCM can be further increased in the collecting duct system secondary to the increased levels of antidiuretic hormone.

In patients with end-stage renal disease, RCM is cleared by extrarenal pathways, as well as by dialysis, because they are not protein-bound and possess relatively low molecular weights. The clearance of these agents by hemodialysis, at blood flow rates between 172 and 250 ml min⁻¹, varies between 65 and 80% following a 4 h treatment (Ackrill et al., 1976; Lehnert et al., 1998; Milman and Christensen, 1974; Schindler et al., 2001; Waaler et al., 1990). The volume of distribution (Vd) of the RCM is limited due to their polar state in physiologic conditions. Reaching equilibrium depends on the following factors: organ blood flow, capillary density and permeability, and interstitial diffusion distances (Burgener and Hamlin, 1981; Dean et al., 1978; Morris and Fischer, 1986; Sage, 1983). Following administration of RCM there is a rapid equilibration across capillary membranes, with the exception of the blood–brain barrier. However, RCM can enter the cerebrospinal fluid through fenestrae in the choroid plexus (Sage, 1983). During the first phase of distribution following RCM administration, there is a rapid fluid shift across the capillary membranes from the interstitial space due to the markedly increased intravascular osmolality (Morris and Fischer, 1986; Sage, 1983; Schiantarelli et al., 1973). It is during this phase that toxicity occurs.

**Mechanisms of Nephrotoxicity**

**Overview**

Nephrotoxicity has plagued the use of RCM since their inception. Through refinement of RCM, this side effect has become less frequent, but it still occurs at alarming rates. The etiology of RCM nephrotoxicity can be broadly grouped into two categories: hemodynamic effects (vasoconstriction) and tubular (cellular) injury both acting in concert. An overall schematic representation integrating these factors and the resulting consequences of RCM administration is summarized in Figure 2. Of these factors, the magnitude of RCM osmolality is central to both the acute hemodynamic and tubular changes following RCM administration (Caldicott et al., 1970; Harvey, 1960; Heyman et al., 1993; Katzberg et al., 1983; Morris et al., 1978; Norby and DiBona, 1975; Talner and Davidson, 1968). Nephrotoxicity from vasoconstriction has been postulated to be responsible for the majority of RCM nephrotoxicity (Bakris and Burnett, 1985; Byrd and Sherman, 1979; Caldicott et al., 1970; Harvey, 1960; Heyman et al., 1993; Katzberg et al., 1983; Larson et al., 1983; Morris et al., 1978; Norby and DiBona, 1975; Talner and Davidson, 1968).

It is well established that delivery of hyperosmolar solution to the renal vasculature results in a biphasic change in renal blood flow (RBF) (Arakawa et al., 1996; Arend et al., 1987; Bagnis et al., 1997; Bakris and Burnett, 1985; Bakris et al., 1990b, 1999; Deray et al., 1990; Drescher and Madsen, 1998; Drescher et al., 1998; Heyman et al., 1988, 1989; Katzberg et al., 1983; Larson et al., 1983; Margulies et al., 1990; Murphy et al., 1998; Schiantarelli et al., 1973; Vare et al., 1988) (Figure 3). After the administration of hyperosmolar solution, there is an initial transient increase in RBF and GFR, followed by a prolonged decrease.
The decrease in RBF is approximately 30–40% of the baseline RBF. Importantly, since similar changes in RBF were reported when hypertonic saline was administered, the hyperosmolar quality of the solution appears to be responsible for the biphasic change in RBF. Furthermore, the reduction in RBF has been shown to correlate positively with the osmolality of the infused solution (Gerber et al., 1979; Katzberg et al., 1977; Mudge et al., 1984). These observations have led investigators to hypothesize that the delivery of a high osmotic load, as associated with RCM administration, to the juxtaglomerular apparatus results in stimulation of a tubuloglomerular feedback processes. This, in turn, reduces GFR by altering the vascular tone of afferent arterioles.

Recovery from the vasoconstriction that follows hyperosmolar RCM injection in normal dogs is universal. However, in three volume-depleted dogs with a 1 and 2/3 nephrectomy there was no recovery from the reduction in RBF, even after 6 h of observation (Figure 4). Such a prolonged effect on RBF supports the clinical observation that volume-depleted subjects with preexisting renal insufficiency are at higher risk for development of acute renal failure after RCM administration.

**Figure 2** A proposed model that amalgamates the proposed mechanisms involved in radiocontrast media (RCM)-induced nephrotoxicity. RCM both reduces renal blood flow and causes tubular injury. In the high-risk patient, for example, renal insufficiency with or without diabetes, the persistent vasoconstriction coupled with direct tubular injury leading to transient intratubular obstruction in a low-flow state combine to yield insurmountable insults to the kidney and, hence, development of renal failure. ↑, increased; ↓, decreased; =, inhibits; +, potentiates; *, SOD does not affect renal hemodynamic responses to RCM but preserves GFR; ET, MF, macrophages; PMN, polymorphonuclear leukocytes; SOD, superoxide dismutase.

**Figure 3** Time course and variability of renal vascular responsiveness between an intrarenal, intraarterial (thoracic aorta), and intravenous bolus injection of an ionic and nonionic radiocontrast media (RCM) in the normal dog. IA, intra-arterial; IR, intra-renal; IV, intravenous.

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In spite of the importance of osmolarity in determining the renal hemodynamic response to RCM administration, there is variability in the vascular effects that is both dose-dependent and influenced by the route of administration (Burgener and Hamlin, 1981; Sage, 1983; Schiantarelli et al., 1973). Figure 3 demonstrates the time course and variability of renal vascular responsiveness between intrarenal, intraarterial (thoracic aorta), and intravenous bolus injection of ionic and nonionic RCM in the dog. These observed renal vascular effects of RCM are also supported by other investigators (Caldicott et al., 1970; Morris et al., 1978; Norby and DiBona, 1975; Talner and Davidson, 1968). Similar observations were made in both femoral blood flow and RBF before and after the administration of both high- and low-osmolar RCM (Figure 5). From these studies, it is apparent that higher osmolar RCM have a higher risk of altered renal perfusion, and consequent renal dysfunction from hemodynamic insults.

The hyperosmolar RCM are also known to have direct toxic effects on renal tubule cells. Several in vitro studies clearly illustrate that hyperosmotic RCM are toxic within minutes to cultured proximal tubular cells (Bhandaru and Bakris, 1995; Humes et al., 1987; Messana et al., 1988a). Enhanced susceptibility to injury of mesangial cells has been demonstrated by comparing high-osmolar (diatrizoate) and low-osmolar (iohexol) RCM. Viability of mesangial cells was reduced to a greater degree under high-glucose conditions. The cytotoxic effects of two different RCM were similar if concentrations were of equivalent osmolality. Interestingly, exposure to mannitol did not influence cell viability unless the culture media contained very high glucose concentration (Wasaki et al., 2001). Other cellular studies, however, also report only minimal cytotoxicity in the presence of low-osmolar RCM (Bhandaru and Bakris, 1995).

In vitro evidence to support the clinical relevance of RCM-induced tubular injury comes from both animal and human studies. Several investigators have shown the presence of granular and hyaline casts in the urine within 2 h following injection of a hyperosmolar RCM (Bhandaru and Bakris, 1995; Mudge et al., 1984; Wasaki et al., 2001). Moreover, renal biopsies from dogs given intrarenal injections of hyperosmolar RCM demonstrate the presence of polymorphonuclear leukocytes and macrophages in the interstitium of the kidney within 3 h of hypertonic RCM injection (see below).

The following discussion focuses on specific factors implicated in both altered renal hemodynamics and tubular injury associated with RCM administration.
Hemodynamic Mechanisms of Nephrotoxicity

The role of calcium in RCM vasoconstriction

Following the elucidation of a biphasic vasospastic response to high-osmolar RCM, investigators have attempted either to block this event or lessen its impact on renal perfusion (Arakawa et al., 1996; Arend et al., 1987; Bakris and Burnett, 1985; Bakris et al., 1990b; Deray et al., 1990; Drescher and Madsen, 1998; Drescher et al., 1998; Heyman et al., 1989, 1993; Katzberg et al., 1983; Larsson et al., 1983; Margulies et al., 1990; Murphy et al., 1998; Vari et al., 1988). Medications evaluated to blunt the vasoconstriction that follows these agents include blockers of the renin-angiotensin system, adrenergic antagonists, calcium antagonists and vasodilators like hydralazine. In each case, these agents have failed to attenuate the vasoconstriction associated with RCM (Katzberg et al., 1983; Morris et al., 1978; Norby and DiBona, 1975; Talner and Davidson, 1968). However, in 1984, calcium channel blockers (CCBs) were reported to ameliorate the RCM-induced vasoconstriction (Bakris and Burnett, 1985). The renal protective effect of dihydropyridine CCBs is thought to depend, in part, on the inhibition of renal autoregulatory mechanisms mediated through the juxtaplomerular apparatus and tubulo-glomerular feedback on afferent arteriolar 'myogenic' responsiveness (Bhandaru and Bakris, 1995; Navar et al., 1986; Wasaki et al., 2001).

Normal rats are resistant to RCM-induced renal injury unless made susceptible (Vari et al., 1988). As nitric oxide (NO) and prostacycline are documented regulators of renal medulla perfusion, pretreatment with i-nitroargininemethylester (-i-NAME) and indomethacin provides an alternative animal model, and does not require surgical intervention. In this model, injection of the high-osmolar RCM, diatrizoate (at doses of 6 or 8 ml kg⁻¹, 306 mg iodine ml⁻¹), resulted in significant, reversible increases in serum creatinine concentration, which is not observed with normal saline or smaller doses of diatrizoate. The effect of this RCM on renal function was greater than with an equal volume of low-osmolar nonionic mono-mertopromide. The CCB, diltiazem (in 2, 6, or 10 mg kg⁻¹ doses), injected intraperitoneally 30 min prior to diatrizoate, reduced the magnitude of GFR decline in a dose-dependent manner (Wang et al., 2001).

CCBs have also been reported to have cytoprotective effects on renal cells; by suppressing influx of extracellular calcium after ischemic or toxic injuries, and by modulating mesangial traffic of macromolecules, they reduce free radical generation and renal hypertrophy (Baer and Navar, 1973; Bakris and Burnett, 1985; Esnault, 2002; Osborne et al., 1923). In addition, CCBs can inhibit the decrease of NO synthesis following RCM administration in humans (Esnault, 2002). Despite this evidence in animal models, the role of calcium channel blockade as a prophylactic agent against RCM in humans remains unproven.

The role of adenosine in RCM vasoconstriction

Adenosine, a well-known vasodilator in the peripheral circulation, acts as a vasoconstrictor in the renal cortex (Hall et al., 1985; Osswald et al., 1978, 1995; Pflueger et al., 2000; Spielman and Thompson, 1995; Tagawa and Vander, 1970; Yao et al., 2001). Furthermore, hypertonc ultrafiltrates, including hyperosmolar RCM, have been shown to induce the release of adenosine from the macula densa cells of the distal tubule (Osswald et al., 1978). Several studies have demonstrated that RBF is altered similarly by both adenosine and hyperosmolar RCM (Arend et al., 1987; Bakris and Burnett, 1985; Deray et al., 1990; Drescher and Madsen, 1998; Hall et al., 1985; Spielman and Thompson, 1995; Tagawa and Vander, 1970). Taken together, the aforementioned data support a central role for adenosine in the mediation of the renal vasoconstrictor response following autorenal hyperosmolar RCM injection. Adenosine has also been shown to be involved in renal autoregulation of tissue perfusion (Hall et al., 1985; Osswald et al., 1978). Inhibition of adenosine activity via an adenosine (A1) receptor antagonist or its production via theophylline attenuates tubulo-glomerular feedback and autoregulation mechanisms (Arend et al., 1987; Osswald et al., 1978, 1995; Tagawa and Vander, 1970).

The major source of adenosine is generation via 5’-nucleotidase, an enzyme activated by low levels of adenosine triphosphate (ATP) (which occurs during periods of hypoxia or ischemia). Adenosine-mediated vasoconstriction, unique for renal tissue, is induced by activation of A1 receptors (predominant on afferent arteriole) and subsequent increase in intracellular calcium. RCM can directly activate A1 receptors, while tubular osmotic load may increase transport mechanisms and ATP hydrolysis, leading to adenosine generation. Moreover, RCM reduces erythrocyte flexibility and activates adhesion molecules and leukocytes to endothelial cells. In diabetics, adenosine-induced vasoconstriction is 20- to 30-fold greater due to attenuated NO-dependent vasodilation, and possibly by upregulation of adenosine A1 receptor density, as well as increased adenosine production by hyperfiltering diabetic kidney (Pflueger et al., 2000).

In an NO-depleted rat model, i-NAMe was given in drinking water for 8 weeks, GFR failed to drop in response to diatrizoate RCM in the presence of a selective adenosine A1 receptor antagonist (KW-3902) administered intravenously 20 min prior to injection. Addition of mannitol had no effect on GFR changes following RCM in these rats (Yao et al., 2001). This suggests that the decrease in GFR was independent of osmotic load. KW-3902 induced a significant increase in urine volume and sodium excretion in addition to that observed by RCM, but it is unknown if this actually reflects a reduction in tubular damage.

The role of endothelin in RCM vasoconstriction

Margulies et al. (1991) were first to demonstrate an increase in both plasma and urinary endothelin concentration following RCM administration in the dog. Unlike other autacoids, such as adenosine, endothelin release is not dependent on RCM tonicity (Harvey, 1960; Heyman et al., 1992; Margulies et al., 1991; Follock et al., 1997). Rather, both in vivo experiments in rats and in vitro experiments using endothelial cell culture have shown that neither iodine concentration nor osmotic content of the RCM alters endothelin release (Margulies et al., 1991). Therefore, the mechanism for increased endothelin concentrations following RCM...
remains unclear. The lack of endothelin release with ioversol (Harvey, 1960) adds an additional layer of complexity. This exception is postulated to result from a lack of endothelial cell stimulation, but has not been investigated. Additional studies in rats have shown that endothelin receptor blockade with continuous infusion of BQ123 blocks the renal vasoconstrictor effects of both low- and high-osmolar RCM (Oldroyd et al., 1994; Pollock et al., 1997). Finally, a study using selective endothelin receptor blockade has also shown efficacy for preventing RCM induced decreases in renal function (Pollock et al., 1997).

These observations, taken together with previous studies, suggest that the vasoconstriction observed immediately after RCM administration is mediated by both adenosine and endothelin. These studies further suggest that there may be potentiation of their vasoconstrictor effects due to RCM-associated decreases in NO (Heyman et al., 1988, 1992). Alternatively, there may be insufficient release of NO to compensate for medullary vasoconstriction in patients with preexisting renal dysfunction.

A1 receptor activation acts via TGF to reduce GFR and cortical blood flow. Just as selective blockade of A1 receptors may be advantageous in AKI secondary to ischemia-reperfusion injuries and septic AKI in mice, (Gallos et al., 2005; Kim et al., 2009; Lee et al., 2004; Lee et al., 2007) selective A1 antagonism may be protective against nephrotoxin-induced AKI, such as CI-AKI (Lee et al., 2006; Vallon and Osswald, 2009). In mice DPCPX, a selective A1 antagonist, or genetic deletion of A1 receptors was protective against CI-AKI. Also, increased serum and urinary excretion of adenosine occurs after intravascular administration of contrast media (Arend et al., 1987).

**Mechanisms of Tubular Injury**

**The role of reactive oxygen species**

Reactive oxygen species (ROS) include the superoxide anion, hydrogen peroxide, hydroxyl radical, and single oxygen. These molecules are released from renal cells in response to various stimuli, and act as paracrine and autocrine stimuli (Baud and Ardaillou, 1986; Baud et al., 1983; Cross et al., 1987; Messana et al., 1988b; Shah, 1989). ROS are released by a variety of different cells, including polymorphonuclear leukocytes, macrophages, and glomerular mesangial cells (Baud and Ardaillou, 1986; Baud et al., 1983; Cross et al., 1987; Shah, 1989). This group of molecules has many functions, including antimicrobial activity. Their production can be inhibited by glucocorticoids and their effects reduced by specific scavengers, such as superoxide dismutase (SOD), glutathione, and dimethyl sulfoxide (Baud et al., 1983; Messana et al., 1988b; Scaduto et al., 1988; Shah, 1989). Renal biopsies performed within 3 h of intrarenal RCM administration confirmed a large influx of polymorphonuclear leukocytes and macrophages in both the glomerular and tubular areas (Arakawa et al., 1996). It is hypothesized that these cells, in addition to mesangial cells, release ROS, which in turn contributes to the tubular injury initially induced by the hyperosmotic properties of RCM (Figure 2).

In vitro investigations utilizing electron spin resonance techniques demonstrated that exposure of human mesangial cells to anionic RCM (diatrizoate sodium) produced an increase in ROS (Figure 6), including both superoxide and hydroxyl radical species. Both types of RCM increased the intracellular peroxide levels produced by mesangial cells; however, D-alpha-tocopherol attenuated only the effect of the hyperosmolar RCM diatrizoate. This suggests that oxidative stress may contribute to injury under hyperosmolar conditions.

Direct tubular toxicity is difficult to measure in a clinical setting. Direct tubule toxicity is reflected by increased urinary excretion of lysosomal enzymes and low-molecular-weight proteins. It is therefore difficult to differentiate between direct toxicity and tubular injury caused by renal ischemia (Katholi et al., 1998). In normal, mildly volume-depleted dogs, the oxygen-free radical scavenger SOD partially blocked the fall in GFR following hyperosmolar RCM treatment, but it had no effect on RBF (Arakawa et al., 1996; Yoshioka et al., 1992) found that the proximal tubular content of SOD was much lower in volume-depleted rats when compared with euvoletic animals. As expected, this group showed the greatest declines in GFR following ionic RCM administration.

![Figure 6](image-url) The electron spin resonance spectra following a hyperosmolar radiocontrast media (RCM), sodium diatrizoate, administered to human mesangial cells. Arrows indicate generation of hydroxyl radicals. Reproduced from Baud, L.; Hagege, J.; Sraer, J.; Rondeau, E.; Perez, J.; Ardaillou, R. *J. Exp. Med.* 1983, 158, 1836–1852.
Quintavelle and colleagues demonstrated that RCM in cultured cells caused a dose–response increase in ROS production, which triggered marked activation of the stress kinases Jun N-terminal kinases 1/2 (JNK 1/2) and p38 and thus apoptosis (Quintavelle et al., 2011). This effect on ROS was significantly attenuated by ROS pre-treatment.

It has also been argued that injection of RCM causes ischemia that decreases pO$_2$. In a separate study, Liss et al. (1997) measured oxygen tension in the rat kidney following intravenous injection of a high-osmolar RCM. They reported a small decrease in pO$_2$ in the renal cortex with a profound decrease (to nearly 45%) in the medulla.

Markers of (Tubular) Renal Injury

Overview

The timely diagnosis of CI-AKI is hampered by the limitations of use of serum creatinine for the diagnosis of AKI. There are four major weaknesses with the use of creatinine. Firstly, it varies considerably with age, lean muscle mass, hydration and muscle metabolism. Secondly, creatinine levels may not change until up to 50% of kidney function is lost. Thirdly, because of tubular secretion of creatinine at lower glomerular filtration rate (GFR) kidney function may be overrated. Finally, and most importantly, creatinine may not accurately depict function until a steady-state equilibrium has occurred, which may take several days. This delay in steady-state equilibrium means that potential CI-AKI may not accurately be diagnosed for 2–5 days. Considering these significant deficiencies, and the fact that an increasing number of patients undergoing coronary angiography have chronic kidney dysfunction, there is a real and immediate need for improved diagnostic tools to detect CI-AKI earlier, prior to possible irreversible renal dysfunction.

Neutrophil gelatinase-associated lipocalin

Neutrophil Gelatinase-associated lipocalin (NGAL) was originally identified as a 25kDa protein covalently bound to gelatinase in neutrophils. It is expressed in very low levels in several human tissues (Supavekin et al., 2003). It accumulates predominantly in the proximal tubule. NGAL has been shown to be produced in the kidney in response to ischemic or nephrotoxic injury in both animals (Devarajan, 2005; Mishra et al., 2004a,b; Mori et al., 2005) and humans (Mishra et al., 2006; Nguyen et al., 2005). It has come to prominence in research examining novel biomarkers in AKI in a range of settings. In a study involving 71 children post-cardiac surgery urinary NGAL levels at two hours was found to be a powerful predictor of AKI (Mishra et al., 2005). In that study, children who subsequently developed acute kidney injury (defined as a 50% or greater elevation in serum creatinine), urine NGAL concentrations increased by more than 20-fold within 2 h of cardiopulmonary bypass and remained elevated for at least 5 days thereafter (the duration of the study). Increases in serum creatinine were first detectable only 2–3 days after surgery. NGAL levels have also been shown to predict grades of AKI in adult cardiac surgery patients (Haase-Fielitz et al., 2009).

Though NGAL is known to be increased in atherosclerotic plaques, and may therefore be released during percutaneous intervention (PCI) irrespective of any acute renal injury, NGAL has also shown promise as an accurate early marker of CI-AKI. Urinary NGAL increases at 2 h post-procedure in patients with baseline CKD (defined as baseline estimated glomerular filtration rate of less than 60 ml min$^{-1}$ per 1.73 m$^3$) (Okumura et al., 2014). Preliminary studies, involving limited patient numbers, suggest that serum NGAL is also a reliable marker for CI-AKI (Bachorzewska-Gajewska et al., 2006; McCullough et al., 2012), though in one trial a baseline NGAL level was recommended as being necessary for the interpretation of NGAL in the evaluation of CI-AKI.

Studies are ongoing investigating whether a volume expansion strategy post-angiography dictated by urinary NGAL levels post-procedurally, could be an effective early intervention to decrease CI-AKI (Schilcher et al., 2011).

Tamm–Horsfall proteins

The Tamm–Horsfall protein is a large glycoprotein normally found only in the ascending limb of the loop of Henle extending into the very early portion of the distal tubule. Its presence in urine indicates tubular injury (Bakris et al., 1990a; Berdon et al., 1969; Hoyer and Seiler, 1987; Patel et al., 1964; Schwartz et al., 1970). The solubility of the Tamm–Horsfall protein in the urine depends on the pH, salt concentration, and concentration of proteins in the urine, as well as other factors (Hoyer and Seiler, 1987).

A number of studies demonstrate increases in urinary levels of Tamm–Horsfall protein following hyperosmolar RCM administration (Bakris et al., 1990a; Berdon et al., 1969; Nicot et al., 1984; Parvez et al., 1990; Patel et al., 1964; Schwartz et al., 1970) and multiple experiments were undertaken to evaluate the role of ROS (Bakris et al., 1990a). Studies conducted in volume-depleted dogs clearly demonstrate that SOD attenuates the increase in urinary Tamm–Horsfall protein, decreases urinary casts, and blunts declines in GFR following hyperosmolar RCM administration (Figure 7) (Bakris et al., 1990a).

Recently, surface-enhanced laser desorption/ionization time-of-flight technology was used to determine urine protein perturbations after RCM administration. In patients with normal renal function, protein patterns returned to normal after 6–12 h, but in patients with impaired renal function, no recovery was noted. Moreover, the renally impaired group displayed increases in peaks at 9.75 and 11.75 kDa, representing heparin-binding epidermal-growth-factor-like factor and beta-2-microglobulin, respectively. Conversely, the peak at 66.4 kDa, identified as albumin, was suppressed. These changes can be attributed to combined glomerular and tubular dysfunction after RCM injection (Hampel et al., 2001).

Cystatin C

Cystatin C (CyC) is a cationic non-glycosylated low-molecular weight cysteine proteinase. It is stably produced by all nucleated cells. It is freely filtered by the glomerulus, and is later reabsorbed and almost completely catabolized in the proximal renal tubule
(Grub, 1992). It does not undergo any tubular secretion. It is more sensitive than serum creatinine as a marker of changes in renal function (Dharnidharka et al., 2002; Newman et al., 1995).

CyC and serum creatinine were measured in 410 consecutive patients with CKD (defined as an estimated glomerular filtration rate of < 60 ml min⁻¹ per 1.73 m²) undergoing coronary or peripheral angiography. A CyC increase of 10% at 24 h was demonstrated to be an early and reliable indicator of CI-AKI versus the gold standard of serum creatinine (Briguori et al., 2010). In this study CyC elevation by 10% at 24 h was also shown to be an independent predictor of major adverse events at 1 year.

**Renal Metabolism**

Numerous studies have investigated the effects of high- and low-osmolar RCM on cellular enzyme activity, prostaglandin production, Na⁺/K⁺-ATPase activity, and renal oxygen metabolism (Brezis et al., 1989; DeRubertis and Craven, 1978; Hardiek et al., 2001; Kako et al., 1988; Kim and Akera, 1987; Lang and Lasser, 1975; Lear et al., 1990; Parvez et al., 1990; Talner et al., 1972; Workman et al., 1983). In general, these studies indicate that there is no reliable urinary enzymatic indicator of RCM injury, with the possible exception of the proximal tubular enzymes alanine amino-peptidase and glutamyl transpeptidase (Parvez et al., 1990). These two enzymes were found in significantly higher concentrations in the urine of patients as early as 24 h following either ionic or nonionic RCM, without any significant increase in serum creatinine concentration. Unfortunately, these studies do not provide follow-up data (>72 h after RCM administration) to assess the clinical predictability of these enzyme markers on the development of renal dysfunction.

Although Na⁺/K⁺-ATPase activity is clearly inhibited by hyperosmolar RCM, the mechanism for this inhibition is unclear (Patel et al., 1964). Data from the laboratory of this chapter’s authors and from three other separate investigators (Lang and Lasser, 1975; Talner et al., 1972; Workman et al., 1983) suggest that RCM-dependent ROS generation may play a role in Na⁺/K⁺-ATPase inhibition. ROS could cause either direct damage or inhibition of the Na⁺/K⁺-ATPase pump or inhibition of enzymatic activity secondary to tubular damage or necrosis.

In dog renal slices, both ionic (diatrizoate sodium) and nonionic (iohexol) RCM significantly reduced ouabain-sensitive Na⁺/K⁺-ATPase, but neither affected mitochondrial ATPase. Moreover, this reduction in Na⁺/K⁺-ATPase activity by RCM was attenuated in the presence of SOD. Decrease of Na⁺/K⁺-ATPase activity by RCM was also observed in in vivo dog studies. Natriuresis following RCM administration (diatrizoate sodium) was lower in dogs pretreated with SOD when compared with control animals (Bakris et al., 1990a).

Experimental studies of LLC-PK1 cells (renal proximal tubule cell of porcine origin) showed that RCM resulted in shrinkage of the cells, but did not alter viability or induce apoptosis (Hardiek et al., 2001). Several additional effects were noted, including cell proliferation (assessed by H-thymidine incorporation) was reduced, mitochondrial dehydrogenase activity was inhibited (compatible with reversible alteration of mitochondrial function), and extracellular adenosine concentration, a marker of cellular stress, was increased. Interestingly, this study also found that the ionic properties of the RCM had a greater impact on altering mitochondrial function than the molecular structure or osmolality (Hardiek et al., 2001).

The effects of RCM, as well as other hypoxic factors, on the medullary thick ascending limb of the loop of Henle have also been evaluated (Brezis et al., 1989; Heyman et al., 1989; Lear et al., 1990; Vari et al., 1988). In unilaterally nephrectomized rats that were treated with indomethacin and administered a hyperosmolar RCM (iothalamate), a significant fall in creatinine clearance was noted after 24 h (Vari et al., 1988). In addition, histological studies in this model demonstrate that the loop of Henle had the
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The greatest amount of histologic injury. Consequently, these and other investigators have speculated that the loop of Henle is the most susceptible area of the nephron to hypoxic injury following ionic RCM injection. This is due to the low serum oxygen tension but high cellular oxygen demand (Brezis et al., 1989; Heyman et al., 1989; Vari et al., 1988).

Prostaglandins

Numerous studies have evaluated the modulatory role of prostaglandins of the E series (PGEs) on renal hemodynamics following RCM administration (Lear et al., 1990; Margulies et al., 1990; Osswald et al., 1995). PGE2 administration has been shown to prevent hypoxic injury to the renal medulla by inhibiting oxygen consumption (Lear et al., 1990). However, prostaglandin inhibition in rats has not been demonstrated to result in RCM-induced renal dysfunction, regardless of the osmotic content of the agent used (Workman et al., 1983). Prostaglandins do not, therefore, appear to play a major role in the pathogenesis of RCM nephropathy under normal conditions. Conversely, prostaglandin inhibition in rabbits with decreased renal mass clearly potentiates the vasoconstrictor response that follows RCM injection (Margulies et al., 1990).

It appears that prostaglandins are primarily important in pathophysiological states that are associated with an increased influence of endogenous vasoconstrictors, such as heart failure, diabetes, or renal insufficiency. Moreover, there are species differences in the prostaglandin response to vasoconstrictors. Therefore, studies evaluating the effects of various RCM on renal physiology need to be performed in pathophysiologically relevant models to provide clinically meaningful data. An appropriate model would be the volume-depleted dog with a 1 and 2/3 nephrectomy.

Animal Models of RCM Nephrotoxicity

Evaluations of the renal hemodynamic effects of RCM have largely been performed in normal dogs, rabbits, or rats. Therefore, any assertions from these studies to renal hemodynamic alterations in pathophysiological states (i.e., congestive heart failure, diabetic nephropathy, cirrhosis) are, at best, speculative.

Initially, only one clinically relevant animal model was developed for investigation of the renal effects of RCM, as well as possible prophylactic measures against these effects. Margulies et al. (1990) evaluated the influence of the RCM Vascoray in dogs with congestive heart failure, which was induced after 8 days of pacing the dogs at the ventricular rate of 250 beats min⁻¹. RCM in the setting of heart failure resulted in a significant and more persistent decline in GFR than under normal circumstances, and this decline was attenuated when atrial natriuretic peptide (ANP) was infused. Unfortunately, a multicenter double-blinded placebo-controlled clinical trial, as well as other studies, failed to show a benefit from ANP for prevention of RCM nephropathy (Allgren et al., 1997; Kurnik et al., 1998).

The rat model of CI-AKI is probably not useful. Data from rat models have been misleading and have resulted in clinical trials that failed to show protection against RCM nephropathy, as is the case with furosemide, endothelin, and ANP. The rat model is particularly refractory to renal hemodynamic changes following large doses of ionic RCM. Furthermore, some studies report that data derived from rat studies are difficult, if not impossible, to reproduce (Margulies et al., 1990). Dog models with 1 and 2/3 nephrectomy or congestive heart failure are closer to resembling human RCM nephropathy; however, even these models lack a good correlation with human disease.

Risk Factors for Human RCM Nephropathy

Renal Insufficiency

By far the most relevant risk factor for predicting the development of RCM nephropathy is the presence of renal insufficiency, that is, a serum creatinine concentration of 1.5 mg dl⁻¹. It is difficult to arrive at an actual incidence of RCM-associated renal dysfunction, largely due to varying definitions among the various studies. This incidence is extended between 0% in a random population and 92% in a high-risk population, that is, those with diabetes or heart failure with preexisting renal insufficiency (Alexander et al., 1978; Barrett et al., 1992; Berg et al., 1992; Berns, 1989; Byrd and Sherman, 1979; Carvallo et al., 1975; Cochran et al., 1983; Cramer et al., 1985; D’Elia et al., 1982; Davidson et al., 1989; Diaz-Buxo et al., 1975; Gale et al., 1984; Gomes et al., 1989; Harkonen and Kjellstrand, 1981; Katholi et al., 1993; Khoury et al., 1983; Kinnison et al., 1989; Krumlovsky et al., 1978; Mason et al., 1985; Parfrey et al., 1989; Pathria et al., 1987; Pelz et al., 1984; Pendergrass et al., 1942; Pendergrass et al., 1955; Pillay et al., 1970; Quader et al., 1998; Roy et al., 1985; Rudnick et al., 1995; Schwab et al., 1989; Shafi et al., 1978; Shieh et al., 1982; Shusterman et al., 1987; Sunnegardh et al., 1990; Taliercio et al., 1986; Teruel et al., 1981; Waybill and Waybill, 2001; Weinrauch et al., 1977).

In a classic retrospective study by Byrd and Sherman (1979), subjects with either advanced age, prior renal insufficiency (serum creatinine concentration >1.6 mg dl⁻¹), dehydration, or hyperuricemia had a greater than 50% risk for developing contrast nephrotoxicity. In cases of repeated administration of RCM within 24 h or the presence of diabetes, the risk was increased by an additional 33 and 37%, respectively.

Since the mid-1980s, a number of well-designed prospective and retrospective studies have evaluated some of the risk factors in patients undergoing arteriographic studies (Barrett et al., 1992; Berg et al., 1992; Cramer et al., 1985; Harkonen and Kjellstrand,
1981; Katholi et al., 1993; Krumlovsky et al., 1978; Rudnick et al., 1995; Shafi et al., 1978; Shieh et al., 1982; Sunnegardh et al., 1990). Some studies have also compared the possible differences in renal effects following hyperosmolar RCM and low-osmolar RCM administration in patients with these and other risk factors (Davidson et al., 1989; Gale et al., 1984; Gomes et al., 1989; Katholi et al., 1993; Khoury et al., 1983; Kinnison et al., 1989; Krumlovsky et al., 1978; Parfrey et al., 1989; Pathria et al., 1987; Roy et al., 1985; Rudnick et al., 1995; Schwab et al., 1989).

A study by Parfrey et al. (1989) documented that the population at highest risk of developing CIN following angiographic study was diabetic patients with preexisting renal insufficiency. The investigators found that, given equal hydration status, the presence of preexisting renal insufficiency alone resulted in a greater than fourfold higher risk for the development of acute renal failure when compared with the normal population. Interestingly, this was not true for diabetes alone.

A large multicenter trial, The lohexol Cooperative Study, confirmed these observations (Rudnick et al., 1995). This study, of 1196 patients who underwent coronary angiography, demonstrated that preexisting evidence of renal insufficiency (serum creatinine concentration $>1.6$ mg dl$^{-1}$) was by far the most powerful risk factor for predicting renal failure following RCM injection. However, the presence of diabetes in subjects with renal insufficiency added to the risk profile. The risk of developing CI-AKI for patients with preexisting chronic kidney disease (CKD) was 21-fold higher than those with normal renal function (Waybill and Waybill, 2001). The risks due to the coexistence of diabetes in subgroups of patients were found to be as follows: diabetes and CKD, 19.7%; diabetes without CKD, 0.6%; CKD alone, 6% (Waybill and Waybill, 2001). Moreover, the study clearly demonstrated that the use of a low-osmolar RCM, instead of conventional RCM, reduced the incidence of renal impairment in those without diabetes but with renal insufficiency (12.2% CIN after using low-osmolar RCM vs 27% after using high-osmolar RCM).

Two additional studies, of participants undergoing coronary artery intervention, evaluated the impact of a low-osmolar nonionic RCM on acute and long-term renal outcomes. In one study, patients with preexisting renal disease were studied (baseline creatinine concentration $>1.8$ mg dl$^{-1}$). CI-AKI was defined as an increase in serum creatinine concentration of at least 25%, and was reported to occur in 37% of the patients within 48 h after the procedure. Independent predictors of renal function deterioration included left-ventricular ejection fraction, contrast volume, and blood transfusions. In-hospital and 1-year mortality for patients without CI-AKI were 4.9 and 19.4%, respectively, compared with 14.9 and 35.4% for those with CI-AKI (22.6 and 45.2% for patients who required dialysis treatment) (Gruberg et al., 2000).

In the second study, CI-AKI was defined as an increase in creatinine concentration of $>0.5$ mg dl$^{-1}$ from baseline, which was observed in 3.3% of patients. The incidence of CI-AKI was associated with baseline creatinine concentration, acute myocardial infarction, shock, and RCM volume, together with age, diabetes, chronic heart failure, and peripheral vascular disease (Rihal et al., 2002). The risk among diabetics was higher only in the subgroup with baseline creatinine concentration of $>2.0$ mg dl$^{-1}$. In-hospital mortality was 22% among patients experiencing CI-AKI, compared with only 1.4% in those without CI-AKI. Among survivors, the history of CI-AKI was associated with greater incidence of myocardial infarction and higher mortality (1-year survival, 12.1%; 5-year survival, 44.6%), compared with patients with no such a history (1-year mortality, 3.7%; 5-year mortality, 14.5%).

The Mehran risk score incorporates the most significant risk factors for CI-AKI (hypotension, intra-aortic balloon pump use, congestive heart failure, chronic kidney disease, diabetes, age >75 years, anaemia, and volume of contrast) which are assigned a weighted integer. The total score is calculated as the sum of each of the weighted integers (Mehran et al., 2004). This score has been shown to predict not only CI-AKI but also poorer short- and long-term outcomes in patients undergoing primary PCI (Sgura et al., 2010).

### Miscellaneous Medical Conditions

A review of several prospective angiographic studies demonstrates that the probability of developing renal impairment following an RCM study is a function of the preexisting level of renal function. Moreover, if concomitant conditions, such as heart failure, diabetes, cirrhosis, or volume depletion, are present, the risk of renal dysfunction is substantially greater (Berns, 1989; Dudzinski et al., 1971; Murphy et al., 2000; Rudnick et al., 1995; Stolker et al., 2010; Waybill and Waybill, 2001). For these groups, a reduced total volume of low-osmolar or iso-osmolar RCM is mandatory (Barrett and Carlisle, 1993).

### Complications of RCM Procedures

#### Atheroembolic Disease

One of the less well-known complications of RCM treatment is the development of atheroembolic-induced renal failure, which mainly occurs with the coexistence of smoking, peripheral vascular disease, age exceeding 50 years, and poorly controlled hypertension with subsequent progressive renal disease (Dudzinski et al., 1971; Kassirer, 1969; Meyrier et al., 1988; Smith et al., 1981; Vogt et al., 2001). Roughly two-thirds of the reported cases occur following a stimulus that triggers showers of microemboli from a damaged aorta (Kassirer, 1969; Meyrier et al., 1988; Smith et al., 1981).

Atheroembolic renal disease is attributed to occlusion of small arteries by fatty-type material from eroded plaques in the diseased aorta. These plaques are dislodged, in part due to the viscous nature of the RCM, and then travel through the renal artery to the arcuate and interlobular arterioles. These plaques occlude the vessels and result in ischemia to the glomerular tuft. Over time, this ischemia results in scarring and nephron loss.
Clinically, skin mottling (livedo reticularis) of the lower extremities, or 'blue toes,' is a common feature of this process (Coburn and Agre, 1993; Colt et al., 1988; Kassirer, 1969; Meyrier et al., 1988; Om et al., 1992; Smith et al., 1981). However, variable presentations, including abdominal pain, gastrointestinal bleeding, or pancreatitis, may also occur (Coburn and Agre, 1993; Colt et al., 1988; Kasinath et al., 1987; Kassirer, 1969; Meyrier et al., 1988; Om et al., 1992; Smith et al., 1981; Thurlbeck and Castleman, 1957). Laboratory indicators to the diagnosis include a transient eosinophilia, hypocomplementemia, and increased sedimentation rate (Kasinath et al., 1987; Kassirer, 1969; Meyrier et al., 1988).

The clinical distinction between RCM-induced nephrotoxicity and atheroembolic renal disease lies in the time course. RCM-induced nephrotoxicity is noted usually within hours, while atheroembolic renal disease has a time course of days to weeks after the procedure (Thurlbeck and Castleman, 1957). In order to minimize the risk of atheroemboli in high-risk subjects, some authors suggest a brachial rather than femoral approach to cardiac catheterizations (Thurlbeck and Castleman, 1957). In this way the aorta, the repository for atheromatous plaques, is avoided.

**Prophylactic Strategies for Prevention**

To achieve true prophylaxis against RCM-induced nephrotoxicity, the clinician must pretreat the patient prior to the injection of RCM. Numerous clinical studies have evaluated various therapeutic interventions shown to prevent declines in renal function in animal models following RCM. Pharmacological interventions investigated include: adequate hydration; loop diuretics at various time periods throughout the contrast study; osmotic diuretics, such as mannitol; CCBs prior to RCM administration; theophylline prior to a contrast procedure, to block adenosine; nonspecific receptor block of endothelin, both of which failed to protect agonist CIN (Allgren et al., 1997; Wang et al., 2000). A summary of prophylactic interventions shown to be effective for reducing the incidence of RCM-induced renal impairment is presented below. Only those procedures that have shown promise or have proven efficacy have been discussed in any depth.

**Efficacious Prophylactic Approaches**

**Hydration**

A decrease in effective circulating volume (volume depletion) is known to magnify the risk factors of RCM-induced renal dysfunction in patients (Byrd and Sherman, 1979; Eisenberg et al., 1981; Louis et al., 1996; Mueller et al., 2002; Solomon et al., 1994; Stevens et al., 1999). Therefore, pretreatment with normal saline should always be considered because it reduces the risk of CI-AKI.

Recommendations include administration of 0.45% saline (1.0–1.5 ml kg\(^{-1}\) min\(^{-1}\)) starting 4 or 12 h before and continuing for 8–12 or 12–24 h after the procedure in patients at moderate or high risk, respectively. Although 0.45% sodium chloride is widely recommended, a recent prospective, randomized, controlled trial tested whether the use of isotonic or half-isotonic hydration would result in any difference to the incidence of CI-AKI (Mueller et al., 2002). The study included 1620 patients (20.7% with CKD, 15.7% with diabetes) who received low-osmolar nonionic RCM during coronary angioplasty. CI-AKI (increase in serum creatinine concentration of at least 0.5 mg dl\(^{-1}\)) developed in 0.7% of patients who received isotonic hydration and in 2.0% of those who received half-isotonic hydration. The superiority of isotonic infusion was more pronounced in patients who underwent elective procedures (CI-AKI in 0.7%, compared with 2.7%), but there was no difference between the two hydration schedules in the subgroup that underwent emergency angioplasty. Women, diabetics, and patients who received 250 ml or more of RCM benefited especially. Risk factors for CI-AKI were female gender and baseline serum creatinine concentration. In their discussion, (Mueller et al., 2002) suggested that the superiority of isotonic saline was due to a more pronounced volume expansion and renin–angiotensin axis inhibition. However, less than 2.0% of patients enrolled had severe CKD (creatinine concentration >1.6 mg dl\(^{-1}\)).

Finally, Krausuki et al. investigated the 250 ml of 0.9% intravenous saline over 20 min on call to elective coronary angiography versus at least 12 h of 5% dextrose in 0.45% saline at a rate of 1 ml kg\(^{-1}\) h\(^{-1}\) before the procedure. In this study of 63 subjects with preexisting CKD all subjects received at least 12 h of intravenous fluids after the procedure. No patient in the 0.45% arm developed CI-AKI, in contrast to 4 of 37 (10.8%) in the bolus arm (\(p = 0.136\)). This study suggests that there may be a benefit to sustained intravenous hydration prior to RCM exposure, however the sample size, discrepancy of fluid types in the two arms limit the applicability of this study (Krasuski et al., 2003).

As noted in a recent review by Weisbord and Palevsky (2008), these studies points to a clear benefit to the administration of isotonic intravenous fluid before and after RCM. As described in the following text, the next debate appears to be the optimal fluid composition (0.9% normal saline vs sodium bicarbonate) and dose/regimen. Comparisons between these regimens is difficult due to the fact that not all other risk factors for CI-AKI were considered in each study. Therefore, no clear evidence exists to stipulate the fluid used, though guidelines recommend commencing the fluid at least 1 h pre-procedure and continuing for 3–6 h after RCM administration (Kidney Disease: Improving Global Outcomes (KDIGO), 2012).
Adenosine antagonists

Clinical studies have evaluated the effects of the adenosine antagonist theophylline for prophylactic use against RCM-induced nephrotoxicity (Erley et al., 1994; Erley et al., 1999; Huber et al., 2001; Katholi et al., 1995; Kolonke et al., 1998). In one randomized, prospective double-blind study, subjects with GFRs below 75 ml min\(^{-1}\) were given either theophylline or placebo 45 min before injection with a low-osmolar RCM (Erley et al., 1994). While the number of participants was small (n = 35), the theophylline group had no significant reduction in renal hemodynamics, compared with a 22% decrease in GFR after low-osmolar RCM alone. A second prospective randomized clinical study of 93 patients with coronary artery disease and serum creatinine concentration of < 2.0 mg dl\(^{-1}\) corroborated the renal protective quality of theophylline (Katholi et al., 1995). Specifically, subjects were administered theophylline at a dose of 2.9 mg kg\(^{-1}\) every 12 h for four doses prior to the RCM study. This regimen was found to prevent renal failure in a high-risk group that received low-osmolar RCM after adequate hydration.

More recent clinical studies support the role of adenosine receptor blockade in the prevention of CI-AKI. Kolonke et al. (1998) studied 58 patients with renal insufficiency who were undergoing angiographic studies. Patients were randomized to 165 mg of theophylline or placebo before injection of a high-osmolar RCM. In the 24 h following the procedure, those who did not receive theophylline showed significant reductions in GFR and increased beta-2-microglobulin excretion.

In the placebo-controlled study by Erley et al. (1999), theophylline (270 mg in the morning, 540 mg in the evening orally started 2 days before and continued for 3 days after RCM) was administered together with hydration to patients with preexisting CKD (serum creatinine concentration > 1.5 mg dl\(^{-1}\)). Serum creatinine concentration and its clearance level did not change significantly: serum creatinine concentration increased by 0.5 mg dl\(^{-1}\) in two patients who received theophylline (5.7%) and in one patient in the placebo group (3.4%). The only difference was a significant reduction of urine N-acetylglucosaminidase in the theophylline group. The authors concluded that theophylline did not afford an additional benefit (Erley et al., 1999). However, theophylline may be beneficial in patients for whom sufficient hydration may be impossible (e.g., congestive heart failure) (Erley et al., 1999).

Conversely, theophylline given intravenously at a dose of 200 mg 70 kg\(^{-1}\) before the injection of low-osmolar RCM in patients hospitalized in the intensive care unit (50% with CKD, 38% diabetics, use of nephrotoxic antibiotics) was associated with reduced incidence of CIN (2%) (Huber et al., 2001). Specifically, serum creatinine concentration remained low 12, 24, and 48 h after RCM exposure. Based on these studies, theophylline, at a dose < 5 mg kg\(^{-1}\) could be started immediately prior injecting RCM, in addition to hydration for patients with CKD.

Based on the aforementioned individual study results, it is not surprising to learn that in a systematic review and meta-analysis performed by Bagshaw and Ghali (which includes all of the above referenced studies), they concluded that theophylline may reduce the incidence of CI-AKI; however, the findings are not consistent across all studies (Bagshaw and Ghali, 2005). They pooled data from nine randomized trials involving 585 patients. The patients who received theophylline had statistically lower serum creatinine values 48 h post contrast compared to the control group (a difference of −0.17 mg dl\(^{-1}\), p = 0.002). However, due to the heterogeneity of results across trials (Q = 9.77, p = 0.08) and no statistical difference in the pooled odds ratio of the development of CIN in those receiving theophylline (0.40 (0.14–1.16); p = 0.09), the benefits of theophylline in preventing CI-AKI remain unclear (Bagshaw and Ghali, 2005). This uncertainty is further highlighted by a separate meta-analysis by Ix and colleagues who found seven randomized controlled trials that examined the capacity of theophylline or aminophylline to prevent CI-AKI. These pooled studies (n = 480) demonstrated that the difference in the mean change in creatinine was lower in the theophylline/aminophylline arm compared with the placebo arm (p = 0.004). However, this same analysis failed to demonstrate a benefit when looking exclusively at those subjects undergoing coronary angiography, and there was only marginal benefit when they limited their analysis to those studies using concomitant intravenous fluid administration (Ix et al., 2004). Finally, in the most recent meta-analysis by Kelly et al. (2008) (6 trials, 330 subjects), theophylline did not demonstrate the ability to reduce the risk of CI-AKI more than intravenous saline alone (relative risk 0.49 (0.23–1.06, p = 0.14)).

Dai et al. evaluated the data from 16 RCTs evaluating the use of theophylline (n = 13) or aminophylline (n = 3) in a meta-analysis in 2012 (Dai et al., 2012a). In most studies theophylline or aminophylline was administered for several hours prior to administration of the RCM and continued for 3–5 days. Based on conventional definitions, there was an overall 52% reduction in incidence of CI-AKI, though there was a non-significant reduction in CI-AKI in patients with baseline CKD (defined as creatinine ≥ 1.5 mg ml\(^{-1}\)). There was a diversity in results noted amongst the trials. Higher quality studies (defined as a Jadad score of ≥ 3) showed a non-significant increased risk of 39% with theophylline/aminophylline, whereas studies of lower quality were associated with a large risk reduction (71%; p < 0.001). Overall, therefore the evidence is low and the balance of risks versus benefit remains uncertain.

Class of contrast medium

Use of low-osmolar or iso-osmolar RCM in combination with modern angiographic techniques (use of carbon dioxide as initial agent and iodinated RCM only when necessary, omission of left ventriculogram whenever possible, obstruction of femoral arteries during lumbar or renal arteriograms, and thus reduction of RCM dose, etc.) lowers the risk of development CI-AKI in patients with preexisting CKD (Aron et al., 1989; Gerber et al., 1982; Higgins et al., 1983; Lufti et al., 2002; Lund et al., 1984; Rieger et al., 2002; Sterner et al., 2001; Townsend et al., 2000).

The landmark meta-analysis by Barrett and Carlisle (1993) demonstrated that low-osmolality contrast (600–800 mOsm kg\(^{-1}\)) provided a significant reduction in the risk of CI-AKI when compared with high-osmolality contrast (1200–2000 mOsm kg\(^{-1}\)).
This 45 trial meta-analysis demonstrated that low-osmolar contrast lead to decreased rates of CI-AKI (increase in serum creatinine $>0.5$ mg dl$^{-1}$) in those with existing kidney injury as well as in those without stable kidney function; the data has been confirmed subsequent analyses (Rudnick et al., 1995). Low-osmolar RCM also offers benefits regarding cardiac effects: fewer arrhythmias, less hypotension, and less interaction with CCBs when compared with hyperosmolar agents (Gerber et al., 1982; Higgins et al., 1983; Shafi et al., 1978; Shihe et al., 1982).

Because of these meta-analyses and clinical trials, the question as to whether everyone should receive low-osmolar RCM has been posed. An early evaluation of the cost–benefit ratios for low-osmolar and hyperosmolar agents did not support the use of low-osmolar RCM in the population at high risk for renal dysfunction (Fischer et al., 1986). However, it is clear from data submitted to the US Food and Drug Administration that low-osmolar RCM is well tolerated in high-risk patients and is associated with a lower incidence of nephropathy and lower overall mortality (Lasser et al., 1997).

The question as to whether iso-osmolar contrast is safer than low osmolar is one than remains intensely debated, despite numerous randomized controlled trials and meta-analyses. The Kidney Disease: Improving Global Outcomes (KDIGO) body attempted to clarify the issue for their recent guidelines. They examined 14 RCTs and felt overall that overall there was no consistent benefit seen in this trials to warrant the recommendation of iso-osmolar contrast over low-osmolar (Kidney Disease: Improving Global Outcomes (KDIGO), 2012).

In a meta-analysis by Heinrich the pooled relative risk in 16 studies analyzing iodixanol with low-osmolar agents was 0.68 (95% CI 0.46–1.01; $p = 0.06$). There was no significant reduction in CI-AKI in studies involving only patients with baseline renal dysfunction after intra-arterial contrast administration, or those involving patients with normal renal function (Heinrich et al., 2009). However, in the 3 studies in which the low-osmolar contrast medium used was iohexol, the incidence of CI-AKI was significantly lower with iodixanol (RR 0.38; 95% CI 0.21–0.68; $p < 0.01$). A further meta-analysis reviewing 25 trials in 3260 patients further supported the fact that the data supporting a reduction in CI-AKI with iodixanol was no longer significant. Guideline writers have noted this change in evidence. The 2012 ACC/AHA focused update of the 2007 guideline on the management of unstable angina/non-ST-elevation myocardial infarction altered the 2007 guidelines recommendation which had listed the use of iso-osmolar contrast agents as class 1 (highest) level of evidence in the management of acute coronary syndromes in patients with preexisting CKD (Anderson et al., 2007). In the 2012 update, no recommendation on use of iso-osmolar or low-osmolar contrast media is offered. The aforementioned KDIGO group state that iso-osmolar or low-osmolar contrast is recommended rather than high-osmolar iodinated contrast agent.

Gadopendate dimeglumine, a gadolinium-based contrast medium, is widely used in magnetic resonance imaging is considered to be an alternative contrast agent for digital subtraction angiography (DSA) (Rieger et al., 2002; Townsend et al., 2000). Its use in patients with severe renal impairment (mean creatinine concentration $3.6$ mg dl$^{-1}$), either alone or with carbon dioxide, was previously thought to be benign and was not noted to be accompanied by any further renal deterioration (Luft, 2002; Rieger et al., 2002; Townsend et al., 2000). A connection between gadolinium use and the development of nephrogenic systemic fibrosis (NSF) has led to increased caution and decreased utilization of this contrast agent in the setting of preexisting kidney disease (Canavese et al., 2008).

**RCM dose adjustment**

It is important to monitor the dose of RCM in order to prevent renal toxicity. Patients with severe renal dysfunction should have an adjustment in the administered dose of RCM. Cigarroa et al. (1989) provided guidelines for dosing with RCM to reduce the risk of RCM-induced nephrotoxicity in patients with renal disease. These investigators demonstrated that appropriate dose reductions of RCM can prevent significant increases in RCM-induced renal dysfunction. The formula they suggest is:

$$\text{RCM limit} = \frac{5 \text{mlRCM} \times \text{kg body weight (max = 300ml)}}{\text{Serum creatinine concentration}}$$

In this study of patients with serum creatinine concentrations of $>1.8$ mg dl$^{-1}$, CIN developed in 2% of the cases with use of limited RCM volume but in 26% of the cases if the limit of quotation was exceeded (Cigarroa et al., 1989). Subsequently, it has been shown that even small volumes of low-osmolar contrast may lead to the development of CIN (Manske et al., 1990).

More recently investigators have sought to determine the ideal ratio of contrast volume to creatinine clearance. A prospective observational study of 3179 consecutive patients undergoing percutaneous coronary intervention demonstrated that a volume of contrast to creatinine clearance ratio $\geq 3.7$ was independently associated with increased risk of CIN (defined as a 0.5 mg dl$^{-1}$ increase in creatinine within 48 h of 200 contrast. The effect persisted after correction for other known CIN risk factors (odds ratio, 95% CI 3.84 (2.0–7.3), $p < 0.001$) (Laskey et al., 2007). Extrapolation of this study has led to the thinking that regardless of the baseline renal function, the volume of contrast received should not exceed twice the baseline glomerular filtration rate.

Finally, some data point to a difference in CIN rates depending on the route of administration of the RCM (intra-arterial vs intravenous); however, these differences have not be borne out in follow-up studies (Campbell et al., 1990).

**Increased urinary flow rate**

The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study demonstrated that increasing urinary flow rate to greater than 150 ml h$^{-1}$ reduced the toxicity of RCM (Stevens et al., 1999). The high urinary flow rate decreases the concentration of RCM in the kidneys, with a rapid transit of RCM through the kidneys and decreases the overall toxic exposure of
the kidneys to the RCM. In analysis of the PRINCE study no patient with a urinary flow rate of greater than 150 ml h\(^{-1}\) had an episode of CI-AKI. The forced diuresis in this trial was achieved with intravenous crystalloid, furosemide, mannitol (if pulmonary capillary wedge pressure < 20 mmHg), and low-dose dopamine.

However, the use of furosemide to decrease CI-AKI has been controversial and in contrast to the findings of the PRINCE trial, a study by Solomon et al (1994) concluded that in patients with CKD undergoing angiography hydration with, hydration with 0.45% saline provided better protection CI-AKI than does hydration with 0.45% saline plus mannitol or furosemide.

The REMDIAL II trial using the RenalGuard system (PLC Medical systems, Inc Franklin MA), demonstrated that hydration with saline and NAC plus a low dose of furosemide controlled by the RenalGuard system was superior to the combination of bicarbonate sodium and NAC in preventing CI-AKI (Briguori et al., 2011). The RenalGuard system has a closed-loop fluid management system consisting of a high-volume fluid pump and a urine collection system which interfaces with a urinary catheter. Urinary flow was set at 300 ml h\(^{-1}\) during the study. This system enables the physician to achieve a high urinary output with a low furosemide dose safely by maintaining the intravascular volume, thereby reducing the risk for over- or underhydrating. In the REMDIAl II trial 30 out of 146 patients in the control group had CI-AKI versus 16 out of 146 in the RenalGuard group (odds ratio 0.47; 95% CI, 0.24–0.92).

**Selective dopamine receptor stimulation**

Some studies have produced data that suggest selective D1 receptor stimulation causes significant increase in GFR, RBF, and natriuresis (Chu and Cheng, 2001; Kini et al., 2002; Tumlin et al., 2002). An animal study evaluated the effect of fenoldopam, a selective D1 receptor agonist, on renal hemodynamics (Bakris et al., 1999). In the study, volume-depleted dogs treated with fenoldopam (0.01 g kg\(^{-1}\) min\(^{-1}\)) 60 min after injection of RCM were found to have a blunted vasoconstriction response and no reduction in RBF and GFR. The action of fenoldopam was confirmed by using a D1 receptor antagonist (Schering 23390) in a separate experimental procedure.

Favorable outcomes for fenoldopam were initially found in uncontrolled (or using historical control) clinical studies and with a small number of patients. In two prospective studies with patients suffering from CKD, fenoldopam reduced the incidence of CIN to 4.5 and 13%, compared with 18.8 and 38% in historical control groups. In both studies hydration with sodium chloride (0.9%) was also used (Chu and Cheng, 2001). Investigators have also tested whether fenoldopam any beneficial effect on preventing CIN in patients with CKD (serum creatinine concentration ≥ 2.0 mg dl\(^{-1}\)) undergoing coronary intervention. The low-osmolar nonionic agent ioversol and hydration with sodium chloride (0.45%, before, during, and after the procedure) were used in all groups. Fenoldopam (0.03–0.1 g kg\(^{-1}\) min\(^{-1}\)) was administered intravenously, starting 15–20 min before and continuing for 6 h after the contrast agent. CI-AKI (increase in serum creatinine concentration more than 25% at 48–72 h or absolute increase greater than 0.5 mg dl\(^{-1}\)) was observed in 3.8% of patients, with no significant difference between diabetics and nondiabetics. Only age (greater than 75 years) was a strong independent predictor for CI-AKI. Other risk factors (diabetes, contrast volume, and baseline creatinine concentration) did not act in a similar way (Kini et al., 2002).

More recently, a controlled multicenter study supported the role of fenoldopam in patients with preexisting CKD (serum creatinine concentration 2.0–5.0 mg dl\(^{-1}\)) after receiving nonionic low- or iso-osmotic RCM. One hour after the procedure, renal plasma flow (RPF) increased by 15.8% in the fenoldopam group and decreased by 33.2% in the control group. The incidence of CI-AKI (21 and 41%) did not reach significant level of difference between the two groups; however, the peak of serum creatinine concentration at 72 h (2.8±0.35 and 3.6±1.0 mg dl\(^{-1}\)) was significantly lower in the fenoldopam group. Data suggested that fenoldopam, unlike dopamine or endothelin blockade, increases the blood flow in both the cortex and the outer renal medulla (the outer renal medulla is thought to be the most susceptible region for contrast toxicity). Further analysis of this study (reduced RPF at 4 h in fenoldopam group) suggests that higher concentrations and longer treatment periods may be necessary to produce a significant effect (Tumlin et al., 2002).

Building on this study, a prospective placebo-controlled double-blind multicenter randomized trial investigated intravenous fenoldopam (0.05 µg kg\(^{-1}\) min\(^{-1}\) titrated to 0.10 µg kg\(^{-1}\) min\(^{-1}\)) versus placebo starting 1 h prior to angiography and continuing for 12 h. This 315 subject trial did not show any decrease in CI-AKI (>25% increase in baseline creatinine within 96 h of contrast), with 33.6% in the fenoldopam group, compared with 30.1% in the placebo arm (p = 0.61). Additionally, there were no differences in 30-day mortality (2.0 vs 3.8%), RRT (2.6 vs 1.9%) or rehospitalization rates (17.6 vs 19.9%) (Stone et al., 2003). Despite these negative results in a well-conducted, controlled trial, subsequent studies have sought to compare the preventative properties of fenoldopam to those of N-acetylcysteine (NAC). These studies offer conflicting results (Allaqaband et al., 2002; Briguori et al., 2004; Ng et al., 2006). To date there is no definitive evidence to demonstrate the utility of fenoldopam in the prevention of CI-AKI, and an adequately powered negative trial suggesting that this is not a useful prophylactic therapy for this indication.

**N-acetylcysteine**

There has been much interest regarding the role of NAC in the prevention of RCM nephropathy. Experimental evidence documented a role for ROS in contributing to RCM nephropathy, and NAC competes with superoxide to limit the production of peroxinitrite while serving as a precursor of glutathione synthesis (to scavenge a variety of ROSs) (Bakris et al., 1990b; Safirstein et al., 2000). Moreover, NAC blocks the expression of vascular cell adhesion molecule-1 and the activation of nuclear factor-kappa B (NF-κB) in mesangial cells. Furthermore, NAC is considered to have vasodilatory properties, probably by increasing NO Synthase activity or by potentiating the biologic effects of NO by reacting with it to form S-nitrosothiol, a more stable and potent vasodilator (Diaz-Sandoval et al., 2002; Safirstein et al., 2000).
The first study reporting favorable effects of NAC was a prospective study by Tepel et al. (2000). The study considered patients with CKD (mean serum creatinine concentration 2.4 mg dl$^{-1}$) who received low-osmolar iopromide for computed tomography imaging purposes. NAC was administered at a dose of 600 mg twice daily on the day before and on the day of the procedure, together with hydration. The incidence of CI-AKI was significantly reduced in the treatment group (2 vs 21% in the control group). In fact, patients who received NAC were found to have serum creatinine concentration values decreased from their baseline 48 h after RCM injection (Tepel et al., 2000). This finding brought about a large degree of speculation as to whether or not NAC had an effect on serum creatinine concentration independent of changes in GFR. In a prospective study, 50 healthy volunteers were administered 600 mg of NAC every 12 h for a total of four doses, and their resulting renal function was measured with serum creatinine, urea, and cystatin C, as well as estimated GFR (eGFR) for up to 48 h following the last dose of NAC (Hoffmann et al., 2004). The results demonstrated that 4 h after the last dose of NAC there was a significant reduction in serum creatinine ($p < 0.05$) with the expected concomitant increase in eGFR ($p < 0.02$). At this same time there was no difference in serum cystatin C levels. This was the first study to suggest an independent effect of NAC on serum creatinine, rather than the presumed ‘renal protective’ effect discussed earlier (Hoffmann et al., 2004). Subsequently, many investigators have sought to replicate and clarify the role of NAC and the possibly artifactual decreases in serum creatinine. Most recently, Haase et al. (2008), conducted a randomized controlled trial of intravenous NAC (300 mg kg$^{-1}$ for 24 h) in 110 cardiac surgery patients by comparing the concentrations of plasma creatinine, cystatin C, and urea as well as the plasma ratio of creatinine to cystatin C. There was no significant difference in the plasma cystatin C, creatinine, or their ratio between those subjects who received NAC ($n = 30$) and those receiving placebo ($n = 80$) (Haase et al., 2008). At the current time, there is no definitive evidence to point to the ability of NAC to alter serum creatinine concentrations independent of GFR/renal function.

This argument aside, NAC has been shown to decrease the rate of CI-AKI results in patients with CKD (serum creatinine concentration 1.4 mg dl$^{-1}$), who received low-osmolar RCM during cardiac catheterization. CI-AKI was detected in only 8% in the NAC group, compared with 45% in the placebo group. The incidence of CI-AKI was associated with use of RCM volume greater than 220 ml. Again, serum creatinine concentration decreased in the NAC group (Diaz-Sandoval et al., 2002).

The usefulness of NAC was also tested in a larger study of 183 patients with CKD who received iopromide for coronary and/or peripheral angiography and/or angioplasty. Lower percentage of patients with NAC (as the regimen by Tepel et al., 2000) developed CI-AKI, 6.5% compared with 11% in the control group, but the difference was not significant. The amount of RCM was independently associated with CI-AKI, and only the subgroup with a low (<140 ml) RCM dose benefited by NAC (0% incidence of CI-AKI, compared with 8.5%) (Briguori et al., 2002).

Marenzi et al. (2006) randomly assigned 354 patients undergoing primary angioplasty to either standard dose (600 mg i.v. before and 600 mg bid for 48 h after), double dose (with 1200 mg in place of 600 mg), or placebo. The serum creatinine increase from baseline was 8% (10/116), 15% (17/119), and 25% (39/119) respectively ($p < 0.001$). The in-hospital mortality was also lower with NAC. 11% of the control group died compared with 4% and 3% in the low and high NAC treatment arms ($p = 0.02$).

The success of these early trials sparked the initiation of several trials to further investigate the merits of NAC in preventing CI-AKI. To date there have been multiple meta-analyses that review these efforts. Note that in the Gonzales et al. (2007) the relative risks are reported based upon cluster I or cluster II. This meta-analysis separated its 22 trials into those demonstrating no benefit (18 trials – cluster I) and those demonstrating a benefit (four studies – cluster II). The trials included in cluster II also demonstrated the aforementioned decrease in serum creatinine concentration (with unclear effect on true glomerular filtration). In the Zagler et al. (2005) meta-analysis, there was a nonsignificant trend toward decreased CI-AKI in those receiving NAC, subgroup analysis showed that those who received NAC prior to a CT scan had a decreased rate of CI-AKI compared to those who had a CT scan with no NAC prophylaxis (relative risk 0.64 (0.42–0.96); data from 7 of 13 trials). In the Pannu et al. (2004) study, there was the smallest of significant effects looking at the entire 1776 patient cohort, but the ability of NAC to protect against CI-AKI could not be replicated or improved upon when performing subgroup analyses on those subjects at highest risk for CI-AKI (CKD, diabetics, etc.). The Doung et al. (2005) study demonstrated a positive overall effect for NAC, but it also showed that the volume of contrast used per patient was higher (174 ml) and thus a potential contributing factor in the positive studies compared to the negative studies (152 ml); mysteriously, the volume of contrast did not play a role in the development of CI-AKI ($p > 0.01$).

Trivedi et al. (2009) performed a meta-analysis of all prospective trials of patients administered high dose NAC (greater than 1200 mg), either orally or intravenously, versus a single periprocedural dose of >600 mg. Their study involved 16 studies and 1677 patients and demonstrated an odds ratio of 0.46 (95% confidence interval [CI], 0.33–0.63) in favor of the higher dose of NAC.

Ten RCTs, including published trials and abstracts, investigating CI-AKI and renal failure requiring dialysis were included in a meta-analysis by Brown et al. (2009). The trials used i.v. NAC or even a combination of oral and i.v. There was also a variation in doses and timing of administration of the NAC. 9 of the studies were comparing a combination treatment of NAC and bicarbonate to NAC and normal saline and one study combined simply compared the combination therapy to NAC alone; one study compared combination therapy with normal saline and NAC, and a separate arm with NAC and ascorbic acid. NAC combined with i.v. bicarbonate reduced CI-AKI by 35% compared to the other above-mentioned combinations. However there was no reduction in CI-AKI requiring dialysis (RR 0.47; 95% CI 0.16–1.41). This meta-analysis concluded that there may be a role for combination-prophylaxis in high-risk patients e.g. those with pre-existing CKD or emergent cases.

Overall, the evidence for NAC in the prevention of CI-AKI remains inconsistent and at times underwhelming. However, it is usually well tolerated and can be considered for high-risk patients.
Sodium bicarbonate

In keeping with the aforementioned attempt to hydrate with isotonic solutions, several studies have investigated the use of sodium bicarbonate in preventing CI-AKI. The hypothesis behind employing bicarbonate (as the anion to pair with sodium) stems from its ability to alkalize the urine and potentially inhibit free-radical formation, which occurs preferentially at acidic pHs (Halliwell and Gutteridge, 1990; Lindinger et al., 2000).

Merten and colleagues were the first to describe the benefits of sodium bicarbonate infusion in the prevention of CI-AKI; in their prospective single-center, randomized trial of 119 patients, hydration with sodium bicarbonate before and after contrast administration lead to decreased rates of CI-AKI (defined as a ≥25% increase in serum creatinine within 48 h of RCM). Patients received either 154 mEq l⁻¹ of sodium chloride or sodium bicarbonate, as a bolus of 3 ml kg⁻¹ h⁻¹ for 1 h prior to iopamidol contrast, followed by an infusion of 1 ml kg⁻¹ h⁻¹ for 6 h after the procedure. CI-AKI occurred in 13.6% (8 of 59) of those who received saline compared with 1.7% (1 of 60) in the bicarbonate group (p = 0.02) (Merten et al., 2004). The trial was stopped early by the local data safety monitoring board, although a strict statistical rule was not applied. Reclassification of a single case could have negated the statistical difference between the groups. On the other hand, a subsequent nonrandomized registry of patients, all of whom received bicarbonate prophylaxis, continued to show a similarly low incidence of CI-AKI. The results of this study were replicated in a smaller single-center prospective randomized unblended trial utilizing the identical fluid supplementation in patients undergoing emergent coronary procedures (Masuda et al., 2007). Serum creatinine (mg dl⁻¹) did not change over the 48 h following RCM administration in those receiving bicarbonate (1.31 ± 0.52 to 1.31 ± 0.59) compared with those who received saline (1.32 ± 0.65 to 1.52 ± 0.92; p = 0.01). Additionally CI-AKI rate were lower in the bicarbonate group, 7 vs 35% p = 0.01 (Masuda et al., 2007).

Since the publication of the study by Merten et al., several studies investigated the effect of bicarbonate infusion on the prevention of CI-AKI. Unfortunately, many of these studies have sought to include sodium bicarbonate hydration as part of a preventive regimen that includes NAC. The RENO trial was a prospective randomized, controlled single center trial investigating hydration with sodium bicarbonate and intravenous NAC administered before and after contrast in patients undergoing percutaneous coronary intervention. CI-AKI (defined as a >0.5 mg dl⁻¹ increase in serum creatinine within 3 days of contrast) occurred in 1.8% of those receiving bicarbonate and NAC compared to 12.7% of those getting isotonic saline (p = 0.032) (Recio-Mayoral et al., 2007). Similarly, in a prospective controlled trial of high-risk (baseline creatinine >1.2 mg dl⁻¹) patients scheduled for cardiovascular procedures, Ozcan and colleagues investigated 3 distinct regimens. Patients received intravenous hydration with sodium bicarbonate or sodium chloride, or sodium chloride plus oral NAC (600 mg twice daily (BID). CI-AKI was defined as a >25% or 0.5 mg dl⁻¹ increase in serum creatinine within 48 h. The rate of CI-AKI was significantly lower the bicarbonate group (4.5%, 4 of 88), compared with the saline only group (13.6%, 12 of 88; p = 0.036), with there being a trend toward less CI-AKI compared to the saline plus NAC group (12.5%, 11 of 88; p = 0.59). Note this trial demonstrates that NAC plus saline offered no added protection as opposed to saline alone (Ozcan et al., 2007).

In the REMEDIAL trial, a prospective randomized three way trial of 326 high risk (creatinine >2.0 mg dl⁻¹ or eGFR <40 ml min⁻¹) subjects comparing 0.9% normal saline/NAC to sodium bicarbonate/NAC to 0.9% saline/ascorbic acid/NAC, the bicarbonate arm appeared to offer a benefit in preventing CI-AKI. CI-AKI (defined as a ≥25% increase of serum creatinine within 48 h) occurred in 1.9% (n = 2 of 108) of the bicarbonate patients, compared with 9.9% (n = 11 of 111) of the saline/NAC arm and 10.3% (n = 11 of 107) of the saline/NAC/ascorbic acid arm (p = 0.019). The REMEDIAL trial utilized iodixanol for all study subjects and demonstrated no statistical difference in the volume of contrast used between the three study arms (p = 0.69) (Briguori et al., 2007). Finally, in a retrospective single-center study of 96 patients who received either bicarbonate and NAC or saline and NAC, there was no difference in CIN rates (12.2% in saline/NAC and 14.9% in bicarbonate/NAC (p = NS) (Schmidt et al., 2007).

The most complete systematic review analyzing trials from 1950 to 2008 was completed by Zoungas and colleagues. It included 23 published and unpublished RCTs of i.v. sodium bicarbonate. Trials with a prespecified endpoint of a creatinine increase of 25% in baseline serum creatinine or an absolute increase of 0.5 mg dl⁻¹ (44.2 μmol l⁻¹) were included. 3563 patients with 396 CI-AKI events were accounted for in the analysis. The pooled RR was 0.62 (95% CI 0.45–0.86). There was heterogeneity noted between published and unpublished studies: RR 0.43 (95% CI 0.25–0.75) versus 0.78 (95% CI 0.52–1.17) respectively.

Similar to NAC, there is a possible, but inconsistent benefit seen with sodium bicarbonate solutions, based on moderate quality data. A multicenter, prospective, randomized, double-blind placebo controlled trial to determine the role of hydration with sodium bicarbonate for the prevention of CI-AKI is warranted.

Statins

There has been growing interest over recent years in the potential use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in reducing the risk of CI-AKI. This renoprotective effect is primarily attributed to the well-established anti-inflammatory properties of statins, but is also related to their ability to improve endothelial function and anti-apoptotic effects (Alpert, 2014). Since 2008, 9 prospective RCTs have been undertaken examining the role of statins in the prevention of CI-AKI (Li et al., 2012a,b; Munoz et al., 2011; Pappy et al., 2011; Quintavelle et al., 2012; Zhang et al., 2011a,b,c; Zhou et al., 2011). There has been considerable heterogeneity in the results of these trials. In 3 of the studies, which assessed moderate to high-dose statins pre-procedure compared with those who did not receive a statin, there was as s significantly lower rate of CI-AKI. A further 3 studies
compared intermediate to high-dose statin therapy to low-dose therapy and found a benefit for the higher doses. However in the other 3 RCTs, statin therapy had no effect on the incidence of CI-AKI.

Recently the first large scale prospective RCTs have been published. Leoncini et al. (2014), studied 504 statin naïve patients with non-ST segment acute coronary syndromes. One group was randomized to 40 mg of rosuvastatin on admission, followed by 10 to 20 mg daily, and the other group received no statin therapy during their hospital stay, but were discharged on a rosuvastatin. The incidence of CI-AKI in the group treated during their hospitalization was 6.7% compared with 15.1% in the untreated group ($p=0.003$). The 30 day composite end-point of MI, stroke, or persistent renal damage was also significantly lower in the treated group. Mortality at 60 days was 3.6% in the statin group, versus 7.9% in the group with delayed treatment ($p=0.07$).

The other RCT studied 2998 patients with type 2 DM, stage 2 or 3 CKD undergoing coronary angiography or percutaneous coronary intervention (Han et al., 2014). Patients were either statin naïve, or had not taken their statin for 2 weeks prior to enrolment. The treatment group were given 10 mg rosuvastatin daily for 2 days prior to the procedure and for 3 days afterwards. The control group did not receive a statin. 2.3% of patients in the treatment group developed CI-AKI, compared with 3.9% in the control arm ($p=0.01$). In contrast with the study by Leoncini which demonstrated that rosuvastatin is effective in patients with mild to moderate CKD, the study by Han found that only patients with moderate CKD (stage 2) benefitted from treatment with rosuvastatin.

**Extracorporeal blood purification**

In the past it had been generally accepted clinical practice to dialyze a patient with end-stage renal disease immediately following an RCM-requiring procedure to eliminate the hyperosmolar RCM. However, about one-third of any given RCM is metabolized and eliminated prior to initiation of dialysis. This movement, which was initially based largely on case reports and clinical experience, has since benefited a number of trials investigating the benefits of prophylactic RRT to reduce the risk of CI-AKI.

Marenzi et al. (2003) performed a prospective randomized controlled trial comparing the benefits of hemofiltration to intravenous hydration with isotonic saline in preventing CI-AKI in 114 patients with serum creatinines $>2.0$ mg dl$^{-1}$. Both interventions were initiated 4–8 h prior to cardiac angiography and continued for 18–24 h post procedure. CI-AKI, defined as a 25% increase from baseline serum creatinine, occurred more frequently in the hydration group (50% of subjects) than in the hemofiltration (2%, $p<0.001$) cohort. Although the authors also demonstrated an in-hospital mortality and 1-year overall mortality, benefit for the hemofiltration cohort caution must be used in the interpretation of these CI-AKI rates as it is well established that hemofiltration will intrinsically decrease serum creatinine concentrations and confound the diagnosis of CI-AKI (Marenzi et al., 2003). Building on this trial, the same group went on to demonstrate that pre- and postprocedure hemofiltration decreased CI-AKI incidence compared to either of the two other regimens: preprocedure hydration with post-procedure hemofiltration, or pre- and postprocedure hydration (isotonic saline). In this prospective randomized three-group trial of 92 subjects with estimated GFRs less than 30 ml min$^{-1}$ undergoing invasive cardiovascular procedures that required RCM exposure, the pre- and postprocedure hemofiltration group also demonstrated an in-hospital mortality benefit ($p=0.03$) (Marenzi et al., 2006). Leaving the effects of hemofiltration on serum creatinine and the lack of validity of the primary outcome of CI-AKI incidence aside, caution must be used in the interpretation of these data as hemofiltration does not remove RCM as efficiently as hemodialysis and the data with regard to hemodialysis is not as definitive. Furthermore, the apparent benefits on CI-AKI incidence and clinical secondary endpoints were only seen in the group that received precontrast hemofiltration in addition to post-procedure hemofiltration, not the latter alone, casting further doubt on the concept that radiocontrast removal is the primary mechanism of any benefit of this approach.

A prospective controlled trial randomized 82 subjects undergoing coronary angiography with concomitant CKD (creatinine $>3.5$ mg dl$^{-1}$) to receive intravenous hydration with isotonic normal saline or prophylactic hemodialysis following RCM exposure (on average initiated 81 min following RCM). This trial, which investigated CI-AKI in advanced CKD, demonstrated a smaller increase in the 72 h postprocedure serum creatinine in the dialysis group ($p=0.01$) as well as a decreased need for short term (in hospital) and chronic dialysis (post discharge) in the prophylactic hemodialysis group ($p=0.018$ for the need for chronic dialysis) (Lee et al., 2007a,b). This recent work is in contrast to the results of several prior studies investigating the role of prophylactic hemodialysis in the setting of RCM administration. A recent systematic review demonstrated no decrease in the incidence of CI-AKI through the perioperative use of of extracorporeal blood purification (Cruz et al., 2006). This review utilized eight trials (six randomized controlled, two nonrandomized), six of which assessed the use of hemodialysis (the other two looked at hemofiltration (Marenzi et al., 2003) and hemodiafiltration. When looking only at those studies investigating hemodialysis (230 total subjects), they were only able to demonstrate a trend toward a decrease in CI-AKI rates (relative risk 1.35 (95% CI 0.93–1.94)).

In conclusion, to date there is no definitive evidence to demonstrate a clinical benefit to the use of extracorporeal blood purification in prophylactic treatment of CI-AKI. Given the costs and logistical difficulties of such an intervention, larger randomized controlled trial of both hemodialysis and hemofiltration are likely warranted.

**Prostaglandins**

In patients with renal impairment, PGE1 (administered at a dose 20 ng kg$^{-1}$ min$^{-1}$ for 6 h, starting prior to RCM) was associated with the lowest elevation in serum creatinine concentration 48 h after a diagnostic procedure. This favorable effect was also
observed in patients with diabetes, who displayed even greater declines in kidney function. Higher doses of PEG1, however, manifested worsening kidney function; arterial pressure decreased resulting in hypotension and further limiting renal perfusion (Koch et al., 2000).

Additionally, in patients with baseline renal dysfunction (serum creatinine $\geq 1.4$ mg dl$^{-1}$) iloprost (PGI2) (2 ng kg$^{-1}$ min$^{-1}$) administered 30–90 min before and terminating 4 h after contrast was found to decrease the rate of CI-AKI (defined as 0.5 mg dl$^{-1}$ or $\geq 25\%$ increase in creatinine on days 2–5 post RCM) compared with the placebo ($p = 0.048$). Unfortunately, a similar effect was not seen at lower doses (1 ng kg$^{-1}$ min$^{-1}$) and the drug was poorly tolerated due to its proclivity to induce hypotension (5 of the 15 subjects receiving the higher dose) (Spargias et al., 2006). Based on its side effect profile (hypotension, nausea and flushing), as well as the scant data demonstrating a benefit, at this time prostaglandin therapy cannot be recommended for the prevention of CI-AKI.

**Ascorbic acid**

There is evidence that ascorbic acid (Vitamin C) may have a role in as a nephroprotective agent in CI-AKI. This benefit is due to its' potent anti-oxidant effect, as well as a potential to nitric oxide bioavailability (Rodrigues et al., 2008) In a meta-analysis Sadat et al. (2013) reviewed data from 9 randomized trials in 1536 patients, ascorbic acid was found to reduce rates of CI-AKI by 33% (risk ratio by random effects model: 0.672; 95% CI, 0.466 to 0.969; $p = 0.034$). Though further prospective RCT are required to further validate the utility of Ascorbic Acid for this indication.

**Other recommendations**

Before RCM is administered in diabetics, it is appropriate to discontinue nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, dipyridamole, as well as metformin (associated with lactic acidosis in cases with renal impairment). Note that in the case of metformin, it may be removed with RRT. It is also suggested that diuretics be withheld 24 h before the procedure. The benefits of intravascular volume repletion will be discussed below. Finally there exists some controversy as to whether agents that exhibit their effect on the renin–angiotensin axis should be held prior to RCM administration. Although some randomized clinical data point to no benefit or harm through their use and nonuse (Rosenstock et al., 2008), larger trials looking at both angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are yet to report their findings.

**Uncertain and nonefficacious prophylactic approaches**

Currently there are no approved pharmacologic agents for the prevention of AKI or, more specifically, CI-AKI.

**Nonefficacious approaches**

Unlike the previously discussed interventions, it is clear from numerous clinical studies that furosemide, mannitol, dopamine, endothelin blockade, calcium channel blockade, and atrial natriuretic peptide fail to offer any additional protection against RCM nephropathy over appropriate hydration and use of low-osmolar RCM (Abizaid et al., 1999; Carraro et al., 1996; Chertow et al., 1996; DeRubertis and Craven, 1978; Hans et al., 1998; Haylor and Morcos, 2001; Kassirer, 1969; Madsen et al., 1998; Meyrier et al., 1988; Murphy et al., 2000; Neumayer et al., 1998; Russo et al., 1990; Smith et al., 1981; Viklund-Spangberg et al., 1996; Vogt et al., 2001; Workman et al., 1983).

**Summary**

Understanding of the mechanisms and pathophysiology of RCM-induced renal dysfunction has only minimally expanded since the mid-1980s. However, large clinical trials have now clearly demonstrated that patients with preexisting CKD, and those who are volume depleted are at highest risk of RCM nephropathy. Moreover, decreased effective circulating volume markedly accentuates the small preexisting risk of RCM nephropathy in people who have diabetes or heart failure. The best evidence consistently supports adequate hydration as the best protection against nephropathy development, along with use of a low- or iso-osmolar RCM and administration of the lowest dose possible for the procedure.

Other measures shown in human studies to be potentially efficacious for reducing the risk include use of either a NAC, selective D1 receptor agonist, adenosine receptor blockade with theophylline. Interventions with no evidence of protection include mannitol, dopamine, furosemide, PGE1 infusion and posttreatment dialysis.

The use of novel urinary and serum biomarkers, particularly NGAL and cystatin C, may improve outcomes in CI-AKI, by their ability to offer earlier confirmation of nephrotoxicity following RCM administration. Though it remains to be demonstrated in clinical trials whether this efficacy in offering a more rapid diagnosis can be translate into improved outcomes.

A proposed scheme for preventing RCM-induced nephrotoxicity is illustrated in Figure 8.
Figure 8  Proposed preventive strategies for prophylaxis against contrast-induced nephropathy (CIN) in all patients based on their baseline renal function. Hydration should be with isotonic solutions (saline or bicarbonate). Some objective measure of hydration status should also be performed. Adjunctive agents shown to be beneficial (in addition to hydration) in those with chronic kidney disease (CKD) and diabetes should be strongly considered. GFR, glomerular filtration rate; NAC, N-acetylcysteine; NSAIDS, nonsteroidal anti-inflammatory drugs; RCM, radiocontrast media.

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