Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art

Simona Detrenis, Michele Meschi, Sabrina Musini and Giorgio Savazzi*

University of Parma, Internal Medicine and Nephrology, Parma, Italy

Keywords: adenosine; contrast-induced nephropathy; endothelial dysfunction; endothelins; intrarenal vascular resistances; low-osmolar and iso-osmolar contrast media

Introduction

A recent report has suggested that contrast media-induced nephropathy (CMIN) is the third highest cause of hospital-acquired acute renal failure [1]. In nearly half of these patients, CMIN occurred during cardiac diagnostic or interventional procedures such as percutaneous coronary intervention. However, considering the amount of contrast media (CM) used today in extracardiac diagnostic procedures, the incidence of nephropathy still remains relatively low. This low incidence may be attributed to the introduction and use of nonionic, low- or iso-osmolar compounds, to the use of smaller volumes of CM and to an increasing awareness of patients who may be at risk for impairment of renal function. The latter is especially true in patients with pre-existing renal failure, diabetes, or both.

Understandingly, the reason a number of patients develop acute renal failure following a cardiac procedure is the necessity to perform these procedures in the presence of pre-existing, and often non-modifiable, risk factors for renal impairment.

Permanent impairment of renal function requiring dialysis can occur in up to 10% of patients with pre-existing renal failure who develop further reduction in renal function after coronary angiography [2], or in <1% of all patients who undergo percutaneous coronary intervention using CM [3]. In-hospital mortality after acute renal failure requiring dialysis in these patients could reach 36% [3], even if this rate might be due to the effects of eventually coexisting comorbidities [4,5].

In most studies, CMIN is defined as an acute decrease in renal function after intravascular administration of CM in the absence of other causes. It is expressed as an increase in serum creatinine levels of 0.5 mg/dl (or 44 μmol/l) or a 25% or greater relative increase from baseline 48–72 h after a diagnostic or interventional procedure [6], even if the clinical significance of this definition in the absence of pre-existing chronic renal failure is questionable.

Nonionic and ionic iodinated contrast media are currently classified, at the concentrations required for diagnostic or interventional radiologic and cardiac procedures, according to their osmolality compared with the osmolality of plasma. The high-osmolar contrast media (osmolality 1500–1800 mOsm/kg) are first generation agents. In fact, the so-called low-osmolar contrast media still have an increased osmolality compared with plasma (600–850 mOsm/kg), while the newest nonionic radiocontrast agents have a lower osmolality, ~290 mOsm/kg, iso-osmolar to plasma (Table 1).

Haemodynamic alterations and tubuloglomerular feedback

The injection of CM induces early, rapid renal vasodilatation followed by prolonged vasoconstriction, with an increase in intrarenal vascular resistances, a reduction of total renal blood flow (RBF) and a decrease in glomerular filtration rate (GFR). Conversely, the effect on the extrarenal vasculature is transient vasoconstriction that precedes a stable decrease in vascular peripheral resistances. The resulting renal ischaemia due to these haemodynamic effects is, in part, responsible for nephropathy [7].

The reduction in renal plasmatic flow is not uniform and occurs especially in the medulla, since medullar perfusion and partial O₂ pressure (PO₂) are much lower than in the cortex. The ascending limb of Henle’s loop in the medulla is characterized by high metabolic activity and increased O₂ demand due to active ion transport through the membrane. Therefore, renal
hypoxia may be a critical factor in the pathogenesis of CMIN [8]. Contrast media are, in fact, potential osmotic diuretics and can cause an increased energy need in the ascending loop. Moreover, CM may be involved in the induction of a plasmatic flow shunt from the medulla to the cortex.

Alterations in regulatory intrarenal and systemic mechanisms, induced by mediators influenced by CM, seem to contribute to the reduced renal perfusion.

Since the urinary concentration of adenosine increases after CM administration, and seems to be related directly to CM osmolality, it is possible that adenosine contributes to the haemodynamic renal biphasic response and therefore to the pathogenesis of CMIN [9,10].

Adenosine passes freely through membranes and induces vasoconstriction via links to A1 receptors, and vasodilatation via links to A2 receptors. This observation seems to be confirmed by the tubuloglomerular feedback mechanism that is activated by an increase in diuresis and natriuresis, secondary to the administration of compounds with high osmolality or tonicity, or both. Due to these compounds, the vasoconstriction of glomerular afferent arterioles causes an increase in intrarenal vascular resistance followed by a reduction in GFR (Figure 1).

The renal vasoconstriction induced by adenosine is accentuated during sodium depletion and is reduced during volume expansion. The interaction between adenosine and endothelins as mediators of renal haemodynamics is not yet well defined. It has been hypothesized that diuresis and natriuresis induced by endothelins play a role in determining increases in renal tissue-related values of adenosine. Experimental studies in diabetic animals have shown increases in adenosine-induced renal vasoconstriction; therefore, the higher incidence of CMIN in diabetics has been attributed to the presumed hypersensitivity of renal vessels to adenosine [11].

Nevertheless, it should be emphasized that a recent study in normal rats seems to point to a lesser role for A1 receptors in the CM-induced reduction of outer medullary RBF [12].

**Endothelial dysfunction**

It has not been shown that contrast media-induced haemodynamic alterations of the renal vessels are directly related to the synthesis and release of active mediators such as nitric oxide and prostaglandins, although their active role in the regulation of renal perfusion is well known. The intrarenal production of these vasodilators is responsible for the maintenance of perfusion and oxygen supply in the medulla; therefore, reductions in the availability of these mediators can promote nephropathy (Figure 2).

A reduction in synthesis or a decreased response to nitric oxide release from the endothelium could be partially responsible for renal ischaemia. It has been suggested that a number of factors are implicated in this decrease in nitric oxide concentration during CMIN, although the role of CM hyperosmolality or of cellular necrosis subsequent to the administration of CM is still doubtful. According to some recent studies, CM could induce a depletion of cofactors involved in nitric oxide synthesis, such as tetrahydrobiopterin, or modify substrates, such as L-arginine [13], or interfere with its synthesis through the nuclear factor κB (NFκB), which inhibits mRNA transcription of inducible nitric oxide synthase. Some authors have suggested that that role is played by vascular impairment of the endothelium, attributable to metabolic conditions (such as hypercholesterolaemia), which subsequently promotes acute renal impairment due to a decrease in nitric oxide after CM administration [14].

Experimental studies conducted in animals showed that prostaglandins (PG) also have a renal vasodilator effect. PGE1 and PGE2 are able to inhibit endothelin transcription implicated in vasoconstrictive mechanisms; PGE1 in particular seems to have a direct cytoprotective effect [15].

It is highly probable that the endogenous vasoactive system of endothelins can contribute to CM-induced ischaemic renal damage. In numerous animal and human models, the administration of CM in large volumes has been followed by increased plasma and urine endothelin levels, especially in the presence of diabetes mellitus and chronic renal failure. The ability of CM to stimulate the release of endothelins is probably unrelated to its osmolality, since endothelin release does not seem stimulated by hypertonic solutions of glucose, mannitol or sodium chloride, either in vivo or in vitro [16]. The evidence of intracellular endothelins confirms the possibility of the release of these mediators from the accumulation site, promoted by highly lipophilic CM that is able to get into the cell. However, the rapid decrease in renal function observed following the administration of CM seems scarcely compatible with the activation of endothelin transcription or with the synthesis of its precursor, or both [17].

The peptidic isoforms of the endothelin family—such as ET1, ET2 and ET3—are synthesized by a conversion enzyme starting from a common precursor. ET1 is produced in the kidney by endothelial cells, glomerular mesangial cells and by the epithelium of the renal tubules. There are two different endothelin receptor subtypes: ET_A, which is located on vascular smooth

**Table 1. Contrast media**

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic, high-osmolal monomers</td>
<td>Iodixanol</td>
</tr>
<tr>
<td>(1500 to 1800 mOsm/kg)</td>
<td></td>
</tr>
<tr>
<td>Ionic, low-osmolal dimers</td>
<td>Ioxaglate</td>
</tr>
<tr>
<td>(600 to 850 mOsm/kg)</td>
<td></td>
</tr>
<tr>
<td>Nonionic, low-osmolal monomers</td>
<td>Iopamidol, Iomepron, Iopromide, Iohexol, Iopentol</td>
</tr>
<tr>
<td>(600 to 850 mOsm/kg)</td>
<td></td>
</tr>
<tr>
<td>Nonionic, iso-osmolal dimers</td>
<td>Iodixanol</td>
</tr>
<tr>
<td>(approximately 290 mOsm/kg)</td>
<td></td>
</tr>
</tbody>
</table>
muscle cells and mediates vasoconstriction; and ET<sub>B</sub>, which is located on endothelial cells and mediates vasodilatation through activating release of nitric oxide and prostacyclin. According to recent observations, both receptors may be involved in increasing vascular resistance [18], while the relative contribution of each receptor to the vasoactive effect could depend upon the specific vascular bed. Endothelins can promote natriuresis and diuresis by reducing the reabsorption of sodium in the proximal tubule (Figure 1).
Experiments on CMIN in animals showed that endothelin receptor antagonists preserve haemodynamic flow and reduce renal vasoconstriction due to the administration of CM. Since this also occurs in the presence of a concomitant inhibition of PG-mediated vasodilatation, it seems likely to support the role played by the endothelin system in CM-induced renal vasoconstriction. However, recent studies in patients with impaired baseline renal function have failed to demonstrate that endothelin receptor antagonists prevent CMIN [19]. A correlation between renal vasoconstriction and the development of nephropathy in humans has not yet been demonstrated.

Vasoactive mediators

In anaesthetized dogs without sodium restriction, pre-treatment with calcium channel blockers widens the initial phase of vasodilatation that follows the administration of CM and cancels the following vasoconstrictive phase [9], thus preventing a reduction in renal flow and GFR. It is therefore likely that the calcium intracellular compartment is involved in the renal vasoconstriction that follows infusion of CM.

The calcium ion has a very important role in both tubuloglomerular feedback and the myogenic response of the afferent arteriole. The increase in intracellular calcium provokes a vasoconstrictive response in intrarenal circulation, and measures to reduce the entry of calcium ions into the animal’s cells prevent the reduction in RBF and GFR secondary to vasoconstrictor stimuli.

A few studies on the action of angiotensin II, also involved in tubuloglomerular feedback, have been done on sodium-depleted dogs, in which this depletion accentuates both the magnitude and duration of the vasoconstrictive phase of the renal blood flow response to injection of CM, and the blockade of the intrarenal renin–angiotensin system shortens the duration of this response [20]. Animal models of acute renal failure have been induced by administration of a CM bolus, following activation of the renin–angiotensin system by sodium restriction and PG synthesis inhibition with indomethacin [21]. Activation of the renin–angiotensin system could cause vasoconstriction of the efferent glomerular arteriole while at the same time increasing the ex novo synthesis of vasodilator prostaglandins resulting in almost stable or slightly increased intrarenal resistance. The CM inhibition of PG synthesis negates the vasodilator response that in turn increases renal resistance, and reduces kidney perfusion and the GFR.

Blood volume expansion and osmotic load following CM injection provoke a release of atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH), respectively, with a counteraction that provokes direct renal effects in vivo. While vasoconstriction induced by ADH can increase CM-induced ischaemia, the vasodilatory effects of ANP may play a protective role. It has been observed that the altered plasma concentrations of these mediators following CM injection are modest and transient; therefore, it does not seem probable that they are the determining cause in the pathogenesis of renal impairment [22]. ANP increases hydrostatic pressure and GFR, with dilatation of the afferent arteriole and vasoconstriction of the efferent arteriole. This peptide blocks tubular sodium reabsorption, induces redistribution of the renal medullar flow, hinders endothelin-induced vasoconstriction and offers resistance to tubuloglomerular feedback. It has been observed that this mediator is capable of preventing renal ischaemia and nephrotoxicity in rats and dogs after CM injection [23]. However, the increased serum concentration of atrial natriuretic peptide does not reach values high enough to prevent vasoconstriction of the afferent arteriole [24].

Haemorheological factors

Experimental studies performed on rats who have undergone CM administration have shown decreases in capillary blood flow in the renal papilla, reductions in erythrocyte velocity and O₂ tension and increases in erythrocyte aggregation (Figure 2). The hypertonic effect of high osmolality CM reduces the volume and deformability of the erythrocyte membrane, contributing to an increase in haemodynamic viscosity and to the worsening of selective medullar hypoperfusion: in fact, the plasma hyperviscosity can alter RBF particularly in the inner medulla, where the haemococoncentration is usually increased. Therefore, most authors agree that the peculiar viscosity of some CM can play a role in the pathogenesis of CMIN, at least in animal studies [25].

Some in vitro studies suggest that osmolality may play a prevalent role in the interaction with platelet degranulation [26] and negative modulation of its effects caused by the ionicity of CM; conversely, other in vitro studies have shown that ionic CM inflict far greater endothelium injury than nonionic CM [27]. Some ionic, high-osmolal monomers seem to cause a release of von Willebrand factor, whereas some ionic, low-osmolal dimers and nonionic, low-osmolal monomers seem to induce an increase in plasminogen activator inhibitor 1. However, the in vivo effects of CM on coagulation, platelet activation and endothelium have not been demonstrated.

Free radicals and reperfusion damage

There is some experimental evidence that reactive O₂ species, such as hydrogen peroxide, hydroxyl radicals, hypochlorous acid and superoxide anion, play a role in CMIN, and that endothelial dysfunction is partly due to oxygen free-radical generation during post-ischaemic reperfusion [28]. Post-ischaemic reperfusion may also lead to re-alkalinization injury, which has been observed after the induction of immediate postischaemic correction in pH value (Figure 3).
During the pathogenesis of CM-induced renal damage an association has been observed between endothelial dysfunction and post-ischaemic syndrome. Alterations in vasoconstriction and perfusion in the external medulla seem to be partially dependent on the production of free radicals and a subsequent decrease in or deactivation of nitric oxide, or both. Free oxygen radicals, particularly the superoxide anion, react with nitric oxide to produce peroxynitrite, an oxidative and very reactive nitrosative species capable of further reducing the bioavailability of nitric oxide, thereby increasing tissue damage. This reactive species also exerts its oxidative and nitrosative effects on the sulfhydryl groups and aromatic rings of proteins, cellular membrane lipids and nucleic acids, and can contribute to the acute vasoconstrictive effects of CM as well: this occurs through the nitrosation of tyrosine residues of enzymes, such as prostacycline synthase and nitric oxide synthase, which are involved in the synthesis of medulla vasodilators. The latter may play a critical role in vascular tone control in the external medulla, where CM ischaemic damage seems to prevail.

In fact, CM administration in humans is followed by increased production of 3-nitrotyrosine, a stable marker of peroxynitrite generation [29]. Patients with chronic renal failure, diabetes mellitus and heart failure show alterations in nitric oxide activity, a fact that may explain the greater susceptibility of these patients to develop CM-induced nephrotoxicity. The positive effects of scavenging free radicals on renal function may be attributed to the prevention of nitric oxide inactivation, particularly during the reperfusion phase.

The connection between vasoactive mediators and free radicals is indirectly demonstrated by the ability of adenosine to induce the production of O₂-reactive species during its metabolization to xanthine and hypoxanthine. Methylxanthines, such as theophylline and aminophylline, could behave both as adenosine antagonist and scavengers of hydroxyl groups and inhibitors of superoxide release. In clinical practice, premedication with methylxanthine before CM administration has not produced satisfying results. There may be evidence that the administration of scavengers, such as superoxide dismutases, before the reperfusion phase could prevent free radical production during reoxygenation [30].

Despite the many animal models of CMIN that provide evidence for the involvement of free radicals, there is only indirect evidence of free radical involvement in humans. In patients with moderate renal failure, the administration of N-acetylcysteine, an antioxidant and scavenger of oxygen free radicals, might reduce the incidence of CMIN, even if this finding has not been uniformly demonstrated by currently available trials [31,32].

**Tubular toxicity and immunological mechanisms**

In an experimental study conducted on isolated mouse proximal tubule segments and cultured proximal tubule cells, the authors made the hypothesis that direct
tubular toxicity may result from alterations in the integrity of the plasma and mitochondrial membranes [33]. Contact of the CM with tubular cells seems to cause a rapid loss of cellular proteins in the suspension medium, including the loss of cell membrane proteins, such as the sodium–potassium ATPase pump and caveolin, as well as mitochondrial proteins, such as cytochrome C. Some authors have also proposed that CM may induce increased susceptibility of the cell membrane to the attack of phospholipase A2, an enzyme able to induce deacylation, which is an important process in ischaemia and cellular hypoxic damage.

The direct cytotoxicity of CM on tubular cells appears to be confirmed by the observed reductions in transepithelial resistance, permeability to substances such as inulin, perturbation of polarized membrane proteins and redistribution inside the cytoplasm of membrane proteins usually related to tight junctions (Figure 3). This damage to renal tubule cells can be accompanied by a significant decrease in tubular potassium and adenosine di- and triphosphate concentration, as well as an increase in calcium content. Furthermore, within 2 h of CM administration, diffused or focal cytoplasmatic vacuolization has been reported, with lysosomal alterations in the proximal convoluted tubule cells and in the internal cortex, and concomitant appearance of enzymuria, which did not affect the other intracellular organelles. Vacuolization seemed to be reversible, with a tendency to resolve within a few days. No relationship has yet been found to exist between the extent of tubular vacuolization and tubular proteins reabsorption or reduction in renal function.

The hypothesis that tubular toxicity is associated with CM hyperosmolality seems to be supported by the potential of other hyperosmolar substances, such as mannitol and hypertonic saline solution, to induce analogous morphological and enzymatic alterations. Moreover, in dogs some CM reduce paraaminohippurate secretion by 30–40%—a fact that is not evident with noniodinated hypertonic solutions. Perhaps CM has a direct toxicity that is unrelated to the effects of hyperosmolality, although no relationship has yet been found to exist between the extent of vacuolization, viscosity or hydrophilicity of the medium used. Finally, since CM modify sodium tubular transport causing intense natriuresis not seen with noniodinated hypertonic solutions, it is possible that damage during sodium transport could be responsible for direct toxicity.

According to a study conducted on renal pig cells, lesions on the proximal tubule could be related to CM-induced inhibition of mitochondrial enzymatic activity [34], which is supported by the observed increase in adenosine concentration and evidence of altered metabolism of ATP. In fact, the adenosine itself could be responsible for contrast-induced tubule toxicity.

The process of cellular death, and in particular apoptosis, as it relates to the genesis of CMIN may also be supported by the correlation between CM administration and reduced cellular proliferation. DNA fragmentation was observed in animal models: it is a marker of apoptosis in cardiac myocytes and renal tubular, glomerular and endothelial cells where nephropathy was experimentally induced by CM administration. Experiments using canine renal cells have demonstrated that the hypertonicity and ionicity of CM plays an important role in cellular death and that this is often associated with increased activity of caspases, enzymes principally involved in cell death [35].

Intratubular precipitation of the Bence Jones protein was one of the first hypotheses to explain CMIN associated with concomitant multiple myeloma. This theory has never been confirmed. In addition, the in vitro precipitation of this protein has been obtained only with ionic high-osmolal CM—seldom used now [36]. It has been confirmed that in vitro CM administration precipitates the Tamm Horsfall protein, which is the major physiological constituent of the urinary casts. Micropuncture experiments using anaesthetized rabbits with CMIN provided evidence of a reduction in the glomerular ultrafiltration coefficient, but did not show an increase in intraluminal tubular pressure, thereby negating the hypothesis of intratubular obstruction.

CM administration has been shown to activate the complement system through an increase in the plasma concentration of C3a, but not of C5a, and these study results have led to the suggestion that the complement system may be activated through the alternative pathway by the direct stimulation of endothelial cells [37]. CM could also stimulate the influx of polymorphonucleates and macrophages in the mesangium: the pathogenesis of CMIN could therefore be partially attributed to the renal infiltration of these cells, with in loco production of free radicals, consequent mesangial contraction and possible mechanically induced reduction in glomerular filtration.

**Physicochemical characteristics of different contrast media**

The experimental evidence obtained thus far after a 70 year search for a less toxic compound indicates that the molecules and the physicochemical characteristics of currently available CM are not comparable. For example, nonionic, low-osmolal, monomeric agents appear to be less nephrotoxic than ionic, high-osmolal agents, at least in patients with pre-existing renal impairment [38]. Some reviewers have hypothesized that nonionic, iso-osmolal dimers can offer some advantages when compared with nonionic, low-osmolal monomers, but there is limited evidence to support this hypothesis in the medical literature [39]. In fact, at present relatively small-scale studies have only compared the nonionic, low-osmolal monomer iohexol with the nonionic, iso-osmolal dimer ioxonam and show a higher incidence of nephrotoxicity with
iohexol compared with iodixanol [40,41], and in particular in diabetic patients with serum creatinine concentrations of 1.5–3.5 mg per decilitre who had undergone angiography [41].

Figure 4 shows the percentage of CMIN reported in patients with mild to moderate renal failure who were administered different nonionic CM. Data were derived from double-blind, randomized comparisons between CM or from the placebo arm of randomized studies on the efficacy of pharmacological prophylaxis with vasodilators and antioxidants. It is necessary to emphasize that the populations enlisted in these trials are not completely comparable because of varying presence of proteinuria, diabetes mellitus, heart failure and concomitant administration of nephrotoxic drugs in each of them.

In these studies, the generally accepted definition of CMIN was either an increase in serum creatinine of 0.5 mg/dl (or 44 μmol/l) or a 25% or greater increase from baseline, 48–72 h after CM injection. The incidence of acute CMIN reported in the medical literature has been verified in 21–26% of patients who received iohexol [38,41,42], in 3–21% who received iodixanol [41,43,44], in 6–12% who received iopamidol [45–47], in 16% who received iomepril [48] and in 11% with iopromide [49]. In the absence of additional trials, CMIN rates with the iso-osmolar agent iodoxanol in high risk patients could be comparable to most of the nonionic low-osmolar agents among which iopamidol, iopromide and iomepril could be provide a particular safety profile based on the reported CMIN incidences.

Clinical perspectives on the prevention of contrast-induced nephropathy

Our knowledge of CMIN is based on a few studies performed in humans and some clinical observations coming from limited, sometimes not homogeneous and not easily comparable patient populations, and on a large number of in vitro and animal experiments. The latter provides important though fragmented information concerning the possible pathogenesis of CMIN.

In the absence of certainties, the quest for modes and methods for the prophylaxis of CMIN in at-risk patients has focused on influencing these presumed pathogenetic events. Information on the mechanisms leading to CMIN is confined to the general consensus that arteriolar renal vasoconstriction plays a fundamental role in its onset and maintenance. Nevertheless, in clinical practice the direct or mediate pharmacologic inhibition of renal vasoconstriction with dopamine, fenoldopam, natriuretic atrial peptide, calcium channel blockers, adenosine antagonists (such as theophylline and aminophylline), prostaglandins and endothelin receptor antagonists has yielded discouraging and unconvincing results or, at most, partial results that require further supporting evidence [19,50–54].

Although all iohexol compared with iodixanol [40,41], and in particular in diabetic patients with serum creatinine concentrations of 1.5–3.5 mg per decilitre who had undergone angiography [41].

Figure 4 shows the percentage of CMIN reported in patients with mild to moderate renal failure who were administered different nonionic CM. Data were derived from double-blind, randomized comparisons between CM or from the placebo arm of randomized studies on the efficacy of pharmacological prophylaxis with vasodilators and antioxidants. It is necessary to emphasize that the populations enlisted in these trials are not completely comparable because of varying presence of proteinuria, diabetes mellitus, heart failure and concomitant administration of nephrotoxic drugs in each of them.

In these studies, the generally accepted definition of CMIN was either an increase in serum creatinine of 0.5 mg/dl (or 44 μmol/l) or a 25% or greater increase from baseline, 48–72 h after CM injection. The incidence of acute CMIN reported in the medical literature has been verified in 21–26% of patients who received iohexol [38,41,42], in 3–21% who received iodixanol [41,43,44], in 6–12% who received iopamidol [45–47], in 16% who received iomepril [48] and in 11% with iopromide [49]. In the absence of additional trials, CMIN rates with the iso-osmolar agent iodoxanol in high risk patients could be comparable to most of the nonionic low-osmolar agents among which iopamidol, iopromide and iomepril could be provide a particular safety profile based on the reported CMIN incidences.

Clinical perspectives on the prevention of contrast-induced nephropathy

Our knowledge of CMIN is based on a few studies performed in humans and some clinical observations coming from limited, sometimes not homogeneous and not easily comparable patient populations, and on a large number of in vitro and animal experiments. The latter provides important though fragmented information concerning the possible pathogenesis of CMIN.

In the absence of certainties, the quest for modes and methods for the prophylaxis of CMIN in at-risk patients has focused on influencing these presumed pathogenetic events. Information on the mechanisms leading to CMIN is confined to the general consensus that arteriolar renal vasoconstriction plays a fundamental role in its onset and maintenance. Nevertheless, in clinical practice the direct or mediate pharmacologic inhibition of renal vasoconstriction with dopamine, fenoldopam, natriuretic atrial peptide, calcium channel blockers, adenosine antagonists (such as theophylline and aminophylline), prostaglandins and endothelin receptor antagonists has yielded discouraging and unconvincing results or, at most, partial results that require further supporting evidence [19,50–54].

Although all iohexol compared with iodixanol [40,41], and in particular in diabetic patients with serum creatinine concentrations of 1.5–3.5 mg per decilitre who had undergone angiography [41].

Figure 4 shows the percentage of CMIN reported in patients with mild to moderate renal failure who were administered different nonionic CM. Data were derived from double-blind, randomized comparisons between CM or from the placebo arm of randomized studies on the efficacy of pharmacological prophylaxis with vasodilators and antioxidants. It is necessary to emphasize that the populations enlisted in these trials are not completely comparable because of varying presence of proteinuria, diabetes mellitus, heart failure and concomitant administration of nephrotoxic drugs in each of them.

In these studies, the generally accepted definition of CMIN was either an increase in serum creatinine of 0.5 mg/dl (or 44 μmol/l) or a 25% or greater increase from baseline, 48–72 h after CM injection. The incidence of acute CMIN reported in the medical literature has been verified in 21–26% of patients who received iohexol [38,41,42], in 3–21% who received iodixanol [41,43,44], in 6–12% who received iopamidol [45–47], in 16% who received iomepril [48] and in 11% with iopromide [49]. In the absence of additional trials, CMIN rates with the iso-osmolar agent iodoxanol in high risk patients could be comparable to most of the nonionic low-osmolar agents among which iopamidol, iopromide and iomepril could be provide a particular safety profile based on the reported CMIN incidences.

Clinical perspectives on the prevention of contrast-induced nephropathy

Our knowledge of CMIN is based on a few studies performed in humans and some clinical observations coming from limited, sometimes not homogeneous and not easily comparable patient populations, and on a large number of in vitro and animal experiments. The latter provides important though fragmented information concerning the possible pathogenesis of CMIN.

In the absence of certainties, the quest for modes and methods for the prophylaxis of CMIN in at-risk patients has focused on influencing these presumed pathogenetic events. Information on the mechanisms leading to CMIN is confined to the general consensus that arteriolar renal vasoconstriction plays a fundamental role in its onset and maintenance. Nevertheless, in clinical practice the direct or mediate pharmacologic inhibition of renal vasoconstriction with dopamine, fenoldopam, natriuretic atrial peptide, calcium channel blockers, adenosine antagonists (such as theophylline and aminophylline), prostaglandins and endothelin receptor antagonists has yielded discouraging and unconvincing results or, at most, partial results that require further supporting evidence [19,50–54].

Although all iohexol compared with iodixanol [40,41], and in particular in diabetic patients with serum creatinine concentrations of 1.5–3.5 mg per decilitre who had undergone angiography [41].
considering analogies with nephropathies of better-known pathogenesis, and without the pretension to reach any certainties or to dictate any interpretations. Considering the fact that multiple biopsies or invasive examinations are for the most part not feasible or ethically acceptable in humans, it may be a long time before definitive and indisputable answers are found regarding the pathogenetic mechanisms of CMIN, although clinical findings on an adequate number of homogeneous patient populations may provide better insight to the problem.

At present, our knowledge concerning renal damage due to radiocontrast agents is still limited since it is affected by a partial vision of the problem. A good history of individual patients at risk, the efficient correction of alterations due to background disease, the detection and correction of dehydration and prophylactic abundant hydration where fluid overload is not contraindicated represent the true preventive measures of CMIN that are available in the year 2005, since pharmacological prophylaxis has proven to be unreliable.

Acknowledgements. The authors thank Mrs Nancy Birch-Podini for reviewing the manuscript.

Conflict of interest statement. None declared.

References