The clinical burden of contrast media-induced nephropathy

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Contrast-induced nephropathy (CIN) is the third cause of acquired acute renal dysfunction. The risk of developing a contrast media (CM)-induced nephropathy depends on their different physicochemical properties. The iso-osmolality of third generation CM lowers the incidence of CM-related renal dysfunction. The tubular effect of CM and the hemodynamic changes induced by CM in the renal medulla are thought to be the main mechanisms of CIN. The percentage of patients at risk has been estimated to range between 3.5 and 15.5% depending on the presence of a preexisting impaired renal function, diabetes mellitus, congestive heart failure, and hypertension and on the volume of contrast used. Currently, only hydration is a generally accepted method of reducing the risk of CIN, and further trials are needed to prove the effectiveness of other potential prophylactic treatments. Alternatives to ordinary CM, such as carbon dioxide or gadolinium chelates, can be used in patients at high risk of CIN undergoing peripheral diagnostic or interventional procedures, thus reducing the occurrence of CIN.

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Contrast media-induced nephropathy (CIN) is a significant but underestimated problem in clinical practice. The use of iodinated contrast media (CM) has increased greatly over the last 30 years, with an estimated 60 million doses applied worldwide each year[1]. With the increasing use of CM in diagnostic and interventional procedures, CIN has become an important cause of iatrogenic acute renal dysfunction, an adverse event associated with a high mortality and among the most costly to treat[1-8]. Since CM have no therapeutic effects themselves, the ideal CM should provide an optimal image quality with no or only minimal adverse events. Nevertheless, despite the development of new molecules with different chemical and physical properties and a reduced toxicity, the problem of acute renal dysfunction still remains an important limitation to their use[9]. Furthermore, an increasing number of patients who may be at risk of developing a CIN are being referred for procedures requiring the use of CM. The clinical burden of CIN is also amplified in the settings of peripheral as well as coronary interventions due to a number of specific issues: intra-arterial administration, repeated injections, high iodine concentrations, the increasingly frequent treatment of complex anatomical situations requiring large volumes of CM and the risk profile of the patients themselves. As a matter of fact, CIN is considered the third leading cause of hospital-acquired acute renal failure, accounting for 12% of all cases[7].

The aim of this article is to review the recent developments in the area of CIN, discussing the potential mechanisms, patients' risk stratification and general approaches to prevention and treatment including the evolution in the profiles of CM. Our purpose is also to stimulate a debate on an often unrecognized pathology among interventional cardiologists, clinical cardiologists and other health professionals who may manage CM or their clinical effects on a daily basis.

Beyond imaging: the physicochemical properties and the physiological effects of contrast media

All CM used in vascular radiological procedures have an iodine-containing benzene ring as the basic chemical structure (Fig. 1). Side chains in positions C1-C3-C5 are important for the physicochemical properties of the compound and should be free of any pharmacological activity. The modification of the side chain in position C3 determines changes in the solubility of the compound, while a modification in position C5 influences the excretion of the compound from the body.

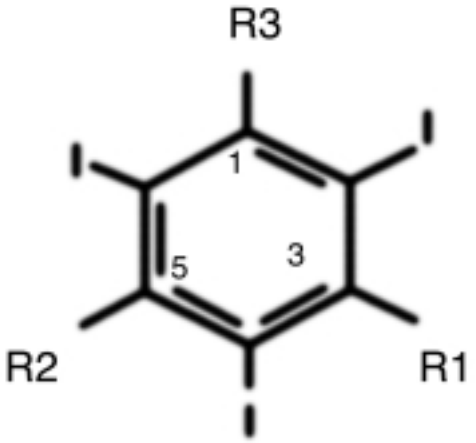

Figure 1. *Basic chemical structure of contrast media. Iodine-containing benzene ring as the basic chemical structure. Side chains (R) in position C1-C3-C5 are important for physicochemical properties.*

The physicochemical properties of CM play a key role in determining their physiological and untoward effects:

• *iodine concentration:* the iodine concentration is reported in mg/ml. A higher iodine concentration enhances both the contrast capacity of the agent and the viscosity of its solution;

• *ionic charge:* CM which dissociate in water solutions have a higher charge and osmolality, variables associated with a higher nephrotoxic effect;

• *hydrophilic properties:* the side chain in position C3 determines the affinity of the compound for water solutions. A high affinity means a more stable compound with less interactions with the cell membranes and a rapid excretion by the kidneys without storage in lipid-rich tissues;

• *viscosity:* it is a parameter of the fluids' dynamics, and depends on the number of particles present in the solution. Blood has a viscosity 5 times higher than that of water, and it may be enhanced by the use of CM. The viscosity of the latter depends on: 1) the temperature of the solution, 2) the iodine concentration, and 3) the dimensions of the particles. Accordingly, the viscosity of CM has to be low to preserve a normal blood flow and hence ensure adequate vascular filling and the avoidance of problems directly linked to a slow flow such as thrombosis. In order to lower the viscosity of CM, it is recommended to warm up the solution to 37°C before its use;

• *osmolality:* this term refers to the number of osmotically active particles per kg of solvent and depends on the size of the molecule of the CM and on the number of particles in solution. CM with a high osmolality determine the passage of water from the tissues to the vascular district and the vasodilation responsible for the warm sensation associated with CM injection. In addition, the use of CM with a high osmolality implies a higher osmotic load on the nephron which may in turn translate into toxic effects.

First-generation CM (Selectan®) included ionic monomers with an ionizing carboxyl group attached to the first carbon of the iodine-containing benzene ring, resulting in a high osmolality (1500-1800 mOsm/kg) and a low contrast power. Second-generation CM such as iohexol (Omnipaque®) were non-ionic monomers with three iodine atoms each molecule[10]. They do not dissociate in water solutions and they may reach an iodine concentration of 320-370 mg/dl with an osmolality of 600-700 mOsm/kg, more than twice the osmolality of blood, and a viscosity 6-7 times higher than that of water. These compounds are more stable and better tolerated by patients compared to first-generation CM[11,12].

Third-generation non-ionic CM are characterized by a reduced osmolality, owing to the fact that they consist of dimers each of which consists of two molecules of CM linked together through a common side chain. This characteristic results in an increase in the size of the molecule in solution but a reduced number of particles present. They can be divided in ionic dimers with a low osmolality such as ioxaglate (Hexabrix®) and non-ionic dimers, such as iodixanol (Visipaque®), which are iso-osmolar with respect to blood.

Due to the large size of the molecules, both types of CM have a higher viscosity which may reduce the flow velocity particularly in small vessels.

The process of minimizing the adverse effects associated with CM administration has focused on lowering their osmolality and altering the ionic nature of these agents whilst maintaining an iodine concentration compatible with radiological examinations, i.e., around 300-350 mg/dl. The physicochemical properties of CM, in particular the higher osmolality of some compounds compared with plasma and their ionic charge, can result in multisystemic effects: osmotic shifts and changes in the ion balance, damage to the vascular endothelial cells which may result in a shift from an anticoagulant to a procoagulant state, hemodynamic and electrophysiological effects and, above all, effects on the renal function. Modern CM are formulated to minimize these effects. In particular, the iso-osmolality of third-generation CM provides a profile that is closer to physiological than conventional CM[13].

Definition and epidemiology of contrast-induced nephropathy

CIN is an important cause of hospital-acquired renal insufficiency which contributes to the in-hospital morbidity and mortality and to the prevalence of end-stage renal disease[7]. It is defined as an acute impairment of renal function manifested by an absolute increase in the serum creatinine concentration (SCrC) of at least 0.5 mg/dl or by a relative increase of at least 25% over the baseline value, in the absence of an alternative etiology[14]. The SCrC typically peaks on the sec-

ond or third day after the procedure and returns to baseline values within 2 weeks. Most of the interventional centers usually discharge patients the day after the procedure and this may result in several missed diagnoses of CIN. The diagnosis of CIN is obvious if the typical course of events follows the administration of the CM. However, other causes of acute renal failure, including atheromatous embolic disease, ischemia and other nephrotoxic factors should always be taken into consideration[14,15]. This is particularly true if significant renal impairment occurs in patients without risk factors for CIN.

The reported prevalence of CIN varies, according to definition and patient subtype, from < 5% where there are no risk factors up to an incidence of 20-30% in patients with risk factors[1,6,16,17]. However, in clinical practice its prevalence may be underestimated because the SCrC is a comparatively insensitive measure of renal function in patients without kidney disease and, furthermore, patients do not always undergo renal function tests prior to and following procedures.

Mechanisms of contrast media-induced nephropathy

The kidney: a target organ for contrast media-induced pathology. The kidneys are susceptible to a toxic challenge for several reasons. Although the kidneys represent only 0.4% of the total body mass, they receive 20-25% of the resting cardiac output per minute, so that blood-borne solutes are rapidly delivered to the renal parenchyma. The renal perfusion is about 5 ml/min/g in the cortex but only 1 ml/min/g in the outer medulla and 0.25 ml/min/g in the papilla[18]. This, coupled with the greater oxygen consumption by the actively transporting cells in the medulla, means that the oxygen tension in the renal medulla is usually close to the level at which the oxygen availability limits the work that cells can accomplish. Under basal conditions, most pO_2 values in the renal medulla are < 30 mmHg, and often around 10 mmHg[19], whereas values in the cortex are 30-70 mmHg, averaging about 50 mmHg[20-22]. Any increase in oxygen consumption, or the administration of agents that limit the cellular uptake or oxygen utilization, will increase the injury to the medullary ascending cells.

The reabsorption of solutes from the luminal fluid increases their concentration in parenchymal cells, and the secretion of other solutes into the luminal fluid increases their concentration near the luminal cell membranes. The counter-current mechanism and the action of antidiuretic hormone further increase the luminal fluid concentrations of solutes. The retention of certain compounds by renal cells increases the duration of toxic exposure. Patients with a reduced nephron population, such as aged patients, excrete solutes through fewer nephrons, thereby increasing the "dose" per nephron. Volume depletion or the obstruction of urine flow may increase the reabsorption of a solute or prolong the exposure of susceptible tissue to a toxic solute[23,24].

Contrast media effects on renal function. Despite the fact that the pathogenesis of CIN is not yet fully understood, two mechanisms are thought to be involved in the process: the tubular effect of CM, and the hemodynamic changes induced by CM in the renal medulla[25].

The structural effect on tubules consists of a vacuolization of the epithelial cells of the proximal segment due to the internalization of CM molecules into lysosomes[26-28]. These effects are not correlated with the CM osmolality but with its viscosity. Dimers, such as third-generation CM, are indeed associated more frequently with these structural changes due to their higher viscosity which may slow down the flow in the tubules and enhance the inner pressure[29]. Patients who received CM have been noted to have an increased urinary excretion of lysosomial enzymes and small molecular weight proteins which are non-specific markers of tubular damage and may be related to the higher osmotic tubular load caused by CM[28]. However, the tubular structural changes are reversible and appear to be less important than the hemodynamic alterations in promoting CIN.

CM appear to induce a biphasic alteration in the renal blood flow with an initially short-lasting increase followed by a decrease resulting from vasoconstriction, an increased intrarenal pressure and a reduced blood cell flexibility[5]. These vascular events are mainly secondary to the direct renal effects of the CM, which modulate the synthesis and release of vasoactive mediators within the kidney[24]. CM interfere with the water and sodium reabsorption by renal tubules, precipitating diuresis and natriuresis. The excess of sodium chloride arriving at the macula densa in the thick ascending limb of Henle's loop activates the tubuloglomerular feedback with the release of mediators which cause vasoconstriction of the afferent and efferent glomerular arterioles and thus reduce the glomerular filtration rate and augment the renal vascular resistance[24,30]. Adenosine, which is a mediator of the tubulaglomerular feedback response, provides the initial increase in renal blood following CM administration by exerting a vasodilator effect by stimulating the A_2 receptors, whereas it acts as a vasoconstrictor via the A_1 receptors in the medulla. In addition, CM may directly determine vasoconstriction by the release of vasoconstrictor endothelin[31]. The release of vasodilators (e.g. prostacyclin, nitric oxide) is important to counteract the vasoconstriction effect and to ensure a sufficient oxygen supply to the medulla. Vasodilation is an endothelium-dependent process and the same mediators may also inhibit tubular transport, thus lowering the oxygen demand whilst augmenting the supply[32,33]. Endothelin and adenosine may act directly as vasoconstrictors or may induce vasodilation via the release of nitric oxide and prostacyclin.

In case of a normal endothelial function, nitric oxide and prostacyclin secretion may ensure an adequate blood flow in the medulla, thus avoiding any ischemic insult. The correct functioning of the homeostatic regulation of the medullary oxygen demand-supply may explain the extremely low rate of contrast nephropathy in healthy patients. In case of an impaired endothelial function, the release of endothelin and adenosine may result in a paradoxical vasoconstriction causing medullary ischemic necrosis[18,34,35]. This observation is supported by the higher incidence of CIN in patients using non-steroidal anti-inflammatory drugs[36] and by the positive effect of theophylline, an adenosine antagonist, in preventing CIN. Furthermore, a recent study demonstrated that diatrizoate and iohexol may induce renal vasoconstriction also causing a selective alteration in the arterial sensitivity to endothelin and nitric oxide[37,38].

In case of loss of the functional renal mass, the compensatory hypertrophy of the remaining nephrons is characterized by hypermetabolism and by higher levels of angiotensin II thus increasing the glomerular filtration in the residual nephrons by a preferential vasoconstriction of the efferent arterial branch. In such a situation, the medullary oxygen demand is increased and the flow-regulatory mechanisms are already active in avoiding ischemic damage to the medulla. The administration of CM in this setting may easily result in a discrepancy between the oxygen demand and supply. In addition, the CM half-life increases in case of renal failure and as a consequence even the CM-related toxic effects are augmented. This explains the higher risk of CIN in patients with an impaired renal function at baseline.

In summary, the synthesis of nitric oxide and prostacyclin guarantees a circulatory homeostasis in the medulla and may prevent an ischemic insult in case of an increased oxygen demand. Accordingly, patients with renal failure, diabetes, hypertension or diffuse atherosclerosis have an impaired endothelial function and consequently are at a higher risk of developing a CIN.

The clinical burden of contrast media-induced nephropathy: approaches to lowering the risk

Risk stratification. The clinical burden of CIN may be minimized by identifying the patients at risk. The percentage of patients at risk has been estimated to range between 3.5 and 15.5%[1]. Several independent patient-related and procedure-related risk factors contribute to the likelihood and extent of CIN. Multivariate analyses of prospective trials have shown that the risk factors for the occurrence of CIN are SCrC or basal creatinine clearance (CrCl), diabetes mellitus, congestive heart failure, and higher doses of contrast used[5,39]. Other risk factors include reduced effective arterial volume (e.g., due to dehydration, nephrosis, cirrhosis) or concurrent use of potentially nephrotoxic drugs such as non-steroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors. Multiple myeloma has been suggested as a potential risk factor for CIN, but a large retrospective study failed to demonstrate an increased risk in these patients[40]. Above all, preexisting renal impairment appears to be the single most important risk factor of CIN: the risk of CIN increases exponentially in relation to baseline SCrC > 1.7 mg/dl. However, in the clinical setting, the relationship between SCrC and glomerular filtration rate may be fleeting, since it is largely dependent on factors which affect muscle mass and creatinine production such as age, sex, and body weight. In patients with diminished muscle mass, even mild elevation in SCrC may reveal significant impairment of renal function. Accordingly, calculation of CrCl may provide better information on renal function (Fig. 2). As in other clinical settings, the presence of multiple risk factors provides an exponential growth of the risk. In one study, the frequency of renal failure rose progressively from 1.2 to 100% as the number of risk factors went from zero to four[41]. Individual patient risk can be estimated from calculated CrCl, diabetic status, and expected contrast dose prior to coronary intervention (Table I).

Using iso-osmolar contrast media to lower the risk of nephropathy. The risk of developing CIN varies according to the physicochemical properties of the CM used. As the renal damage associated with CM largely results from the diuretic and hypertonic effects on the kidney, which are in turn related to the agent's osmolality, it is not surprising that the risk of renal impairment is greatest with the use of high-osmolar CM (HOCM), moderate with low-osmolar CM (LOCM) and low with iso-osmolar CM. Since the introduction of second-generation CM in 1980, several studies have been performed to test whether a non-ionic LOCM was associated with a lower rate of CIN than that observed following the use of an ionic HOCM.

The results of these studies were conflicting due to the different clinical settings in which they were performed. In Schwab's prospective study of 443 patients undergoing cardiac catheterization, 8% of those who received a LOCM developed CIN vs 10.2% of the patients who received a HOCM[42]. A large meta-analysis of 24 trials demonstrated that in patients with a normal renal function who received a HOCM the pooled odds of a rise in the creatinine levels > 0.5 mg/dl was only 0.75, indicating that HOCM were not associated with an increased risk of CIN in this patient population[43]. In their large prospective study of 1196 patients, Rudnick et al.[16] also found that, in non-diabetic patients with a normal renal function, there was no greater incidence of CIN in patients who received a HOCM vs those who received a LOCM (8.2 vs 8.5%, p = NS). Anyway, even in the aforementioned early studies, when a high-risk patient population was considered, the use of HOCM was associated with a higher rate of CIN with respect to that ob-

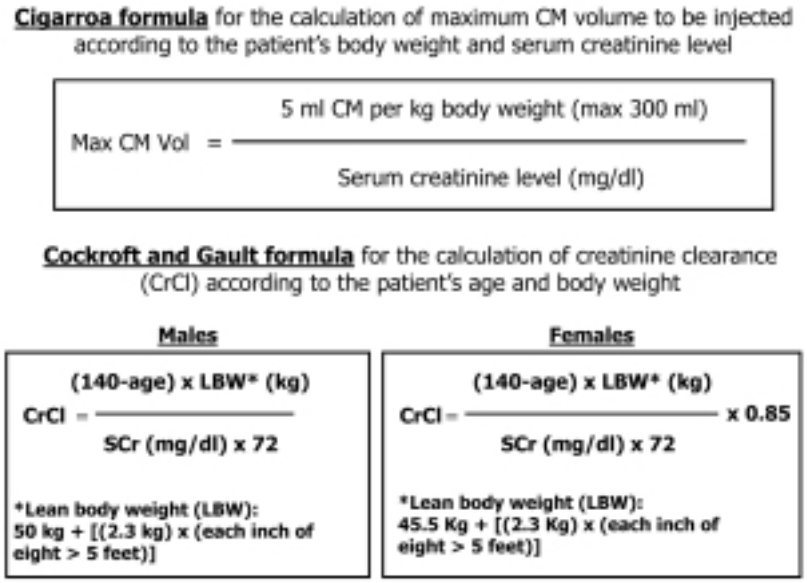

Figure 2. *Cigarroa and Cockroft-Gault formulas for the calculation of maximum contrast medium (CM) volume to be injected and patient's creatinine clearance. SCr = serum creatinine.*

Table I. Risk stratification.

High	SCrC > 1.7 mg/dl or CrCl < 25 ml/min 1.3 < SCrC < 1.7 mg/dl or 50 ml/min < CrCl < 25 ml/min Plus: presence of diabetes, age > 70 years, large volume of CM planned, presence of heart failure, multiple myeloma, dehydration, recent CM administration
Moderate	1.3 < SCrC < 1.7 mg/dl or 50 ml/min < CrCl < 25 ml/min 50 ml/min < CrCl < 75 ml/min Plus: presence of diabetes, age > 70 years, large volume of CM planned, presence of heart failure, multiple myeloma, dehydration, recent CM administration
Low	CrCl > 75 ml/min 50 ml/min < CrCl < 75 ml/min and no risk factors

CM = contrast medium; CrCl = creatinine clearance; SCrC = serum creatinine concentration.

served following the administration of LOCM. Rudnick et al.[16] reported an incidence of CIN up to 27% in non-diabetic patients with underlying chronic renal insufficiency who received a HOCM vs 12.2% in patients who received a LOCM. The lower nephrotoxicity of iso-osmolar CM in comparison with LOCM has now been demonstrated in patients who are at high risk for CIN: those with both an impaired renal function and diabetes mellitus. The first report by Chalmers and Jackson[44] demonstrated a slight but significant reduction in renal function impairment provided by iodixanol (Visipaque®) vs iohexol (Omnipaque®) (15 vs 31% respectively, $p < 0.05$) in 124 consecutive patients with an impaired renal function. These results were confirmed in the recent landmark NEPHRIC study[45], a randomized double-blind trial involving 129 patients with diabetes and a SCrC ranging between 1.5 and 3.5 mg/dl, assigned to iodixanol or iohexol. The increase in the SCrC was significantly lower in patients receiving iodixanol (0.13 vs 0.55 mg/dl from day 0 to day 3, $p = 0.001$) and no patients in the iodixanol group showed an increase of 1.0 mg/dl vs 15% in the iohexol group. The incidence of CIN, defined as an increase in the SCrC ≥ 0.5 mg/dl, was 3% in the iodixanol group and 26% in the iohexol group. The odds of a CIN were 11 times higher with iohexol than with iodixanol. The results of this study indicate that iodixanol significantly reduces the risk of CIN in patients with a preexisting renal impairment and diabetes mellitus. The overall risk of developing nephropathy was lower than that seen in any previous study with LOCM alone in patients at risk, and lower than or comparable with the results reported in studies using potential prophylactic treatments such as fenoldopam or N-acetylcysteine in combination with LOCM.

Volume of contrast media. The volume of CM injected directly correlates with the risk of developing a CIN[1,46]. Rather than having linear characteristics, the relationship between the dose and the risk of nephropathy is probably characterized by a threshold effect related to the underlying renal function. An interesting study randomized patients with a baseline SCrC > 1.8 mg/dl in two groups: in one group the contrast volume was unlimited and in the other group the usable contrast volume was limited according to the patients' body weight and SCrC (the formula is reported in figure 2). The results showed a significant reduction in the occurrence of CIN in the volume-controlled group (2 vs 26%, $p < 0.05$) although all patients who developed a CIN were diabetics[46]. The amount of contrast injected depends on the complexity

of the procedure and on the operator's experience. It is important to address the fact that the progress in interventional techniques and materials enhanced the standard-lesion complexity, allowing optimal results even in case of difficult lesions. The treatment of multivessel disease, challenging chronic total occlusions and extensively diseased coronary segments may require high doses of CM to provide an optimal image quality, thus enhancing the potential toxic effects on the renal function. In addition, angiographic procedures are more often performed in aged patients who are known to be at a higher risk of developing a CIN[47]. These observations prompt accurate decision-making before planning a complex procedure in a patient at a high risk for a CIN.

General prophylactic approaches. An improved understanding of the pathogenesis of CIN has led to the development of a variety of potential prophylactic approaches. One of the most well established and straightforward is hydration, demonstrated in animal studies to inhibit the functional and pathological abnormalities of CIN[48].

Patients at a high risk for a CIN should receive hydration therapy before and after the procedure, in order to maintain a positive fluid balance with a high urine flow rate. This strategy has been shown to be beneficial in different studies[49,50]. In addition, hydration may be achieved orally for the first 12 hours before the procedure (patient out of the hospital) followed by intravenous hydration for the 12 hours following the procedure with the same clinical benefits as a 24-hour intravenous treatment[51].

The comparative efficacies of different hydration regimens have not been extensively investigated, but a recent study in 1620 patients undergoing coronary angioplasty has suggested that isotonic hydration with 0.9% saline is superior to the more often used half-isotonic hydration[52].

Although it reduces the concentration of the CM in the plasma, prophylactic hemodialysis does not lower the risk of CIN[53]. Diuretics such as furosemide, postulated to lessen medullary ischemia, have not proven effective in controlled studies and their routine use is not recommended[50]. The activation of the DA-1 dopamine receptor increases the renal blood flow, but results with dopamine have been conflicting, perhaps as a consequence of its non-specific stimulation of receptors other than DA-1[43,54,55].Weisberg et al.[43] tested the potential benefits of dopamine infusion in diabetic azotemic patients undergoing angiography with the result of an increase in the occurrence of CIN with respect to patients who did not receive the medication. This observation was further confirmed by Abizaid et al.[55]. This paradoxical effect has been attributed to an increase in renal flow more directed towards the cortex than towards the medulla, resulting in a sort of blood stealing. Similarly, the utility of atrial natriuretic peptide remains to be established[56].

A more promising dopaminergic agent, fenoldopam, with selective DA-1 activity and recently approved for the treatment of hypertension, is able to increase the renal perfusion and glomerular filtration rate. Particularly, the effect of fenoldopam is strictly dependent on nitric oxide and its diuretic property is strongly attenuated with the intrarenal infusion of a nitric oxide-synthase inhibitor. The results from non-randomized studies performed in single institutions report a beneficial effect of the use of this drug in preventing CIN[57-59]. More definitive evidence with this agent should be forthcoming from an ongoing randomized trial[60]. Adenosine, a renal vasoconstrictor, is thought to be involved in the pathogenesis of CIN, but outcomes with the adenosine antagonists theophylline and aminophylline have been conflicting. The initial positive effect demonstrated by Erley et al.[61] in terms of renal function preservation, was not confirmed by Abizaid et al.[55] and by Erley[62] himself in a further study. Nevertheless, a recent randomized trial investigating the role of theophylline in reducing the incidence of CIN in high-risk patients showed that theophylline prophylaxis (200 mg) significantly reduced the incidence of CIN with respect to controls (4 vs 16%, $p = 0.046$)[63,64].

The prophylactic oral administration of the antioxidant N-acetylcysteine to patients with renal impairment has been investigated on the assumption that reactive oxygen species are involved in CIN. A randomized trial evaluated the beneficial effects of saline infusion plus oral acetylcysteine (600 mg twice daily for 2 days) vs saline alone in high-risk patients (SCrC > 1.2 mg/dl or CrCl < 50 ml/min) undergoing coronary computed tomography with iopromide, a non-ionic LOCM. The results showed a clear benefit of acetylcysteine administration (a rise in the SCrC ≥ 0.5 mg/dl in the 48 hours following the procedure was observed in 2% in the acetylcysteine group vs 21% in the controls, $p = 0.01$)[65]. However, in the setting of coronary interventions the results obtained are more conflicting and thus, the effectiveness of acetylcysteine remains unclear[66-69].

Some promising results[70] have been obtained by the use of hemofiltration for the prevention of CIN after a coronary intervention. This has prompted the evaluation of this technique on a large scale.

In summary, in terms of general measures, currently only hydration is a generally accepted method of reducing the risk of CIN, and further trials are needed to prove the effectiveness of other potential prophylactic treatments. In addition, the selection of the specific CM used for procedures, especially in patients at risk, may significantly contribute to lowering the risk of nephropathy. Recommendations for the prevention of CIN in high-risk patients are shown in table II.

Alternatives to contrast media

For patients at a high risk of developing a CIN undergoing digital subtraction angiography there are reason-

Table II. Recommendations for prevention of contrast-induced nephropathy in high-risk patients.

All patients undergoing angiography should have SCrC measured
Patients' risk stratification should be performed
Patients with risk factors and normal SCrC should have CrCl measured also
Patients at high risk:
NSAIDs should be discontinued and metformin in diabetics also
Think before acting the expected CM volume necessary for the procedure
Try to use alternative imaging modality (carbon dioxide or gadolinium angiography)
Minimize CM volume injected
Use LOCM (iodinaxol)
Administer isotonic hydration pre- and post-procedure eventually in association with acetylcysteine
Check urine output and SCrC at 24 hours and if increased check until normal value is restored. When acute renal failure occurs, consult a nephrologist

CM = contrast medium; CrCl = creatinine clearance; LOCM = low-osmolar contrast medium; NSAIDs = non-steroidal anti-inflammatory drugs; SCrC = serum creatinine concentration.

able alternatives to the use of iodinated CM. Carbon dioxide angiography is an evolving technique which is now almost comparable to iodinated contrast images. Several studies reported the positive results of carbon dioxide angiography for diagnostic as well as interventional peripheral artery procedures and its main advantages are the absence of allergic reactions and of renal toxicity[71-79]. Other potential candidates as alternatives to iodinated CM in digital subtraction angiography are gadolinium chelates, although the results are still confusing[79,80].

Prognostic impact of contrast-induced nephropathy

The development of a CIN is associated with an increase risk of both in-hospital and long-term adverse cardiac events.

A study by McCullough et al.[81] evaluated the relation between CIN and CIN requiring dialysis and the mortality in 1826 patients undergoing a percutaneous coronary intervention. The incidence of CIN requiring dialysis was rare (< 1%) but the in-hospital mortality was as high as 35.7% and the 2-year survival was only 18%. In a more recent retrospective study investigating the prognostic impact of acute renal failure after a percutaneous coronary intervention, the in-hospital mortality was 22% in patients who developed a CIN vs 1.4% for those who did not. In addition, among hospital survivors with a CIN, the 1- and 5-year mortality rates were 12.1 and 44.6% respectively, i.e. much greater than the 3.7 and 14.5% mortality rates observed in patients without a CIN ($p < 0.0001$)[1].

The randomized trial of CM utilization in high-risk coronary angioplasty (COURT) compared the clinical impact of two different third-generation CM, ioxaglate and iodixanol by evaluating the in-hospital incidence of major adverse cardiac events. The results showed that the endpoint was less frequent in those patients in whom iodixanol was used compared to those receiving ioxaglate (5.4 vs 9.5%, $p = 0.02$). In addition, the angiographic procedure was more frequently successful in the iodixanol group (92.2 vs 85.9%, $p = 0.004$)[82].

Conclusions

CIN is a common, although often under-recognized, problem in patients with preexisting renal impairment especially in case of the coexistence of diabetes mellitus. It is a costly complication, prolonging hospitalization and potentially necessitating dialysis. Recent trials have suggested that its prognostic impact is ominous. Clinical and interventional cardiologists must be aware of this syndrome and familiar with all the effective preventive measures. The clinical burden of CIN may be, in fact, reduced by a careful risk stratification, making sure that these patients are well hydrated, that the contrast doses are minimized and that CM with a more favorable renal profile are administered.

References

1. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105: 2259-64.
2. Turney JH. Acute renal failure - a dangerous condition. JAMA 1996; 275: 1516-7.
3. Deray G, Mouquet C, Ourhama S, et al. Effects on renal haemodynamics and tubular function of the contrast medium ioxaglate in renal transplant patients. Clin Radiol 1995; 50: 476-8.
4. Brezis M, Epstein FH. A closer look at radiocontrast-induced nephropathy. N Engl J Med 1989; 320: 179-81.
5. Barrett BJ. Contrast nephrotoxicity. J Am Soc Nephrol 1994; 5: 125-37.
6. Berg KJ. Nephrotoxicity related to contrast media. Scand J Urol Nephrol 2000; 34: 317-22.
7. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39: 930-6.
8. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. JAMA 1996; 275: 1489-94.
9. Sandler CM. Contrast-agent-induced acute renal dysfunction - is iodixanol the answer? N Engl J Med 2003; 348: 551-3.
10. Metys R, Hornych A, Burianova B, Jirka J. Influence of triiodinated contrast media on renal function. Nephron 1971; 8: 559-65.
11. Almen T. Development of nonionic contrast media. Invest Radiol 1985; 20 (Suppl): S2-S9.
12. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; 175: 621-8.
13. Carraro M, Malalan F, Antonione R, et al. Effects of a

dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol 1998; 8: 144-7.
14. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism - a critical review. Am J Kidney Dis 1994; 24: 713-27.
15. Brady HR, Singer GG. Acute renal failure. Lancet 1995; 346: 1533-40.
16. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. Kidney Int 1995; 47: 254-61.
17. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 1990; 89: 615-20.
18. Heyman SN, Reichman J, Brezis M. Pathophysiology of radiocontrast nephropathy: a role for medullary hypoxia. Invest Radiol 1999; 34: 685-91.
19. Brezis M, Agmon Y, Epstein FH. Determinants of intrarenal oxygenation. I. Effects of diuretics. Am J Physiol 1994; 267 (Part 2): F1059-F1062.
20. Leonhardt KO, Landes RR. Urinary oxygen pressure in renal parenchymal and vascular disease. Effects of breathing oxygen. JAMA 1965; 194: 345-50.
21. Brezis M, Heyman SN, Dinour D, Epstein FH, Rosen S. Role of nitric oxide in renal medullary oxygenation. Studies in isolated and intact rat kidneys. J Clin Invest 1991; 88: 390-5.
22. Brezis M, Heyman SN, Epstein FH. Determinants of intrarenal oxygenation. II. Hemodynamic effects. Am J Physiol 1994; 267 (Part 2): F1063-F1068.
23. Brezis M, Dinour D, Greenfeld Z, Rosen S. Susceptibility of Henle's loop to hypoxic and toxic insults. Adv Nephrol Necker Hosp 1991; 20: 41-56.
24. Brezis M, Rosen S. Hypoxia of the renal medulla - its implications for disease. N Engl J Med 1995; 332: 647-55.
25. Heyman SN, Rosen S, Brezis M. Radiocontrast nephropathy: a paradigm for the synergism between toxic and hypoxic insults in the kidney. Exp Nephrol 1994; 2: 153-7.
26. Tervahartiala P, Kivisaari L, Kivisaari R, Virtanen I, Standertskjold-Nordenstam CG. Contrast media-induced renal tubular vacuolization. A light and electron microscopic study on rat kidneys. Invest Radiol 1991; 26: 882-7.
27. Moreau JF, Droz D, Noel LH, Leibowitch J, Jungers P, Michel JR. Tubular nephrotoxicity of water-soluble iodinated contrast media. Invest Radiol 1980; 15 (Suppl): S54-S60.
28. Humes HD, Hunt DA, White MD. Direct toxic effect of the radiocontrast agent diatrizoate on renal proximal tubule cells. Am J Physiol 1987; 252 (Part 2): F246-F255.
29. Ueda J, Nygren A, Hansell P, Ulfendahl HR. Effect of intravenous contrast media on proximal and distal tubular hydrostatic pressure in the rat kidney. Acta Radiol 1993; 34: 83-7.
30. Osswald H, Muhlbauer B, Schenk F. Adenosine mediates tubuloglomerular feedback response: an element of metabolic control of kidney function. Kidney Int Suppl 1991; 32: S128-S131.
31. Margulies KB, Hildebrand FL, Heublein DM, Burnett JC Jr. Radiocontrast increases plasma and urinary endothelin. J Am Soc Nephrol 1991; 2: 1041-5.
32. Morcos SK, Epstein FH, Haylor J, Dobrota M. Aspects of contrast media nephrotoxicity. Eur J Radiol 1996; 23: 178-84.
33. Agmon Y, Peleg H, Greenfeld Z, Rosen S, Brezis M. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. J Clin Invest 1994; 94: 1069-75.
34. Cantley LG, Spokes K, Clark B, McMahon EG, Carter J, Epstein FH. Role of endothelin and prostaglandins in radiocontrast-induced renal artery constriction. Kidney Int 1993; 44: 1217-23.
35. Touati C, Idee JM, Deray G, et al. Modulation of the renal effects of contrast media by endothelium-derived nitric oxide in the rat. Invest Radiol 1993; 28: 814-20.
36. Heyman SN, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S. Early renal medullary hypoxic injury from radiocontrast and indomethacin. Kidney Int 1991; 40: 632-42.
37. Murphy ME, Tublin ME, Li S. Influence of contrast media on the response of rat renal arteries to endothelin and nitric oxide: influence of contrast media. Invest Radiol 1998; 33: 356-65.
38. Dzgoeva FU, Kutyrina IM. Endothelin-1 in the mechanisms of the nephrotoxic action of X-ray contrast media. Ter Arkh 1997; 69: 39-43.
39. Barrett BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993; 188: 171-8.
40. McCarthy CS, Becker JA. Multiple myeloma and contrast media. Radiology 1992; 183: 519-21.
41. Rich MW, Crecelius CA. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. Arch Intern Med 1990; 150: 1237-42.
42. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. Nephron 1992; 62: 413-5.
43. Weisberg LS, Kurnik PB, Kurnik BR. Dopamine and renal blood flow in radiocontrast-induced nephropathy in humans. Ren Fail 1993; 15: 61-8.
44. Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. Br J Radiol 1999; 72: 701-3.
45. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ, for the Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003; 348: 491-9.
46. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989; 86: 649-52.
47. Byrd L, Sherman RL. Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review. Medicine (Baltimore) 1979; 58: 270-9.
48. Solomon R. Contrast-medium-induced acute renal failure. Kidney Int 1998; 53: 230-42.
49. Eisenberg RL, Bank WO, Hedgock MW. Renal failure after major angiography can be avoided with hydration. AJR Am J Roentgenol 1981; 136: 859-61.
50. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331: 1416-20.
51. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction. A randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest 1998; 114: 1570-4.
52. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002; 162: 329-36.
53. Sterner G, Frennby B, Kurkus J, Nyman U. Does post-angiographic hemodialysis reduce the risk of contrast-medium nephropathy? Scand J Urol Nephrol 2000; 34: 323-6.
54. Hans SS, Hans BA, Dhillon R, Dmuchowski C, Glover J.

Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. Am Surg 1998; 64: 432-6.
55. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol 1999; 83: 260-3.
56. Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 1998; 31: 674-80.
57. Chamsuddin AA, Kowalik KJ, Bjarnason H, et al. Using a dopamine type 1A receptor agonist in high-risk patients to ameliorate contrast-associated nephropathy. AJR Am J Roentgenol 2002; 179: 591-6.
58. Hunter DW, Chamsuddin A, Bjarnason H, Kowalik K. Preventing contrast-induced nephropathy with fenoldopam. Tech Vasc Interv Radiol 2001; 4: 53-6.
59. Madyoon H, Croushore L, Weaver D, Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. Catheter Cardiovasc Interv 2001; 53: 341-5.
60. Stone GW, Tumlin JA, Madyoon H, et al. Design and rationale of CONTRAST - a prospective, randomized, placebo-controlled trial of fenoldopam mesylate for the prevention of radiocontrast nephropathy. Rev Cardiovasc Med 2001; 2 (Suppl 1): S31-S36.
61. Erley CM, Duda SH, Schlepckow S, et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kidney Int 1994; 45: 1425-31.
62. Erley CM, Duda SH, Rehfuss D, et al. Prevention of radiocontrast-media-induced nephropathy in patients with preexisting renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol Dial Transplant 1999; 14: 1146-9.
63. Huber W, Ilgmann K, Page M, et al. Effect of theophylline on contrast material-nephropathy in patients with chronic renal insufficiency: controlled, randomized, double-blinded study. Radiology 2002; 223: 772-9.
64. Kapoor A, Kumar S, Gulati S, Gambhir S, Sethi RS, Sinha N. The role of theophylline in contrast-induced nephropathy: a case-control study. Nephrol Dial Transplant 2002; 17: 1936-41.
65. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000; 343: 180-4.
66. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. J Am Coll Cardiol 2002; 40: 298-303.
67. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA 2003; 289: 553-8.
68. Boccalandro F, Amhad M, Smalling RW, Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Catheter Cardiovasc Interv 2003; 58: 336-41.
69. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J Am Coll Cardiol 2002; 40: 1383-8.
70. Assanelli EM, Marana I, Campodonico J, et al. Prevention of radiocontrast nephropathy after percutaneous coronary intervention by hemofiltration in chronic renal failure patients: in-hospital and 1-year follow-up results. (abstr) Am J Cardiol 2002; 90 (Suppl 6A): 363.
71. Atar E, Neuman-Levine M. Carbon dioxide angiography. Harefuah 1998; 135: 392-3.
72. Beese RC, Bees NR, Belli AM. Renal angiography using carbon dioxide. Br J Radiol 2000; 73: 3-6.
73. Caridi JG, Stavropoulos SW, Hawkins IF Jr. Carbon dioxide digital subtraction angiography for renal artery stent placement. J Vasc Interv Radiol 1999; 10: 635-40.
74. Caridi JG, Hawkins IF Jr, Klioze SD, Leveen RF. Carbon dioxide digital subtraction angiography: the practical approach. Tech Vasc Interv Radiol 2001; 4: 57-65.
75. Culp WC, McCowan TC, Goertzen TC, Habbe TG. Carbon dioxide angiography: complications and pseudocomplications. J Vasc Interv Radiol 1999; 10: 100-1.
76. Dimakakos P. Digital subtraction angiography based on carbon dioxide, technique and clinical application. (letter) Vasa 2000; 29: 89.
77. Gahlen J, Hansmann J, Schumacher H, Seelos R, Richter GM, Allenberg JR. Carbon dioxide angiography for endovascular grafting in high-risk patients with infrarenal abdominal aortic aneurysms. J Vasc Surg 2001; 33: 646-9.
78. Rolland Y, Duvauferrier R, Lucas A, et al. Lower limb angiography: a prospective study comparing carbon dioxide with iodinated contrast material in 30 patients. AJR Am J Roentgenol 1998; 171: 333-7.
79. Spinosa DJ, Matsumoto AH, Angle JF, et al. Gadolinium-based contrast and carbon dioxide angiography to evaluate renal transplants for vascular causes of renal insufficiency and accelerated hypertension. J Vasc Interv Radiol 1998; 9: 909-16.
80. Rieger J, Sitter T, Toepfer M, Linsenmaier U, Pfeifer KJ, Schiffl H. Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. Nephrol Dial Transplant 2002; 17: 824-8.
81. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103: 368-75.
82. Davidson CJ, Laskey WK, Hermiller JB, et al. Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. Circulation 2000; 101: 2172-7.