

Is radiocontrast-induced nephropathy avoidable? The scientific evidence in 2006

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Abstract: Due to the wide use of radiocontrast agents (RCA) in modern radiology and interventional cardiology, the incidence of radiocontrast-induced nephropathy (RCIN) is increasing. The risk factors for RCIN are primarily pre-existing (even mild) renal dysfunction, diabetes mellitus, absolute or relative hypovolemia, nephrotoxic drugs, etc., particularly in elderly patients. The presence of these risk factors seems to be more important than the type of contrast agent used. To date, there are several certainties and controversies in the prevention of RCIN. Hydration with normal saline and/or bicarbonate administration pre- and post-intervention is certainly useful. Though controversial, N-Acetylcysteine administration may be still advisable. Recent investigations showed the benefits of aminophylline/theophylline administration in RCA-induced renal tubular toxicity. Conventional hemodialysis cannot prevent RCIN, but may potentially aggravate renal dysfunction through hemodynamic instability. “High-flux” hemodialysis and hemodiafiltration may contribute efficiently to RCIN prevention, but systematic use of these modern dialysis techniques is limited by high costs and availability. The authors review - in a systematic manner, and in the perspective of evidence-based medicine - the most important data from literature concerning the prevention of RCIN. © Versita Warsaw and Springer-Verlag Berlin Heidelberg. All rights reserved.

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1 Introduction. The medical and social impact of radiocontrast-induced nephropathy

In the age of modern medicine, with the wide usage of imagistic investigations, radiocontrast-induced nephropathy (RCIN) has become an important cause of acute renal failure (ARF). RCIN is a public health issue, due to the high incidence - about 150,000 cases per year in the United States. At least 1% of patients with ARF due to radiocontrast agents (RCA) nephrotoxicity require acute dialysis; hospital stay is prolonged with an average of 17 days in these patients [1]. This leads to supplementary costs evaluated to 32 billion USD/year in the United States alone. Even in cases with mild radiocontrast renal toxicity, not requiring dialysis, the extension with just 2 days of hospital stay leads to supplementary annual costs of 148 million USD [1, 2]. Therefore, prevention of RCIN by identifying those patients at high risk and proper prophylaxis using some simple methods is essential. We discuss below the main data offered by evidence-based medicine regarding the prevention of RCA-induced ARF.

2 Epidemiology

The incidence of RCIN after RCA exposure varies from 0 to 100%, depending on the definition and the type of population studied. In non-diabetic patients with normal renal function, the incidence of RCIN is about 2%, while in subjects with mild renal dysfunction, the incidence of this complication rises to 7% [3]. In patients with both diabetes mellitus and chronic renal failure, the risk for RCIN rises dramatically – over 50% [4]. As the incidence and prevalence of diabetic nephropathy are continuously rising, and cardiovascular complications (requiring investigation with RCA) have epidemic proportions in these patients, the incidence of RCIN will probably increase significantly, in the absence of an efficient prevention strategy.

Although the risk for *severe* ARF requiring dialysis is relatively low (0.5-2%) after contrast agents exposure, it is associated with a catastrophic prognosis: in-hospital mortality of 36% and 2 year-survival of only 19%. About 50% of these cases will require chronic dialysis. It should be mentioned that, no matter if permanent or temporary dialysis is necessary, in these clinical setting, prognosis is poor. The rate of intra-hospital mortality in severe ARF due to RCA is similar to the death rates in severe ARF from other causes – 25 to 76% [2, 5–11] – see Table 1.

3 Risk factors for radiocontrast-induced nephropathy

The main risk factors associated with RCIN are listed in Table 2. The most important risk factor for ARF due to RCA is *pre-existent renal dysfunction* – mostly due to chronic kidney disease, rarely to acute renal failure of various etiologies [5]. For current practice, it is mandatory to emphasize that frequently patients with significant renal dysfunction (creatinine clearance <60 ml/min/1.73 m²) may have “normal” values of serum creatinine

Table 1 The impact of radiocontrast agents nephrotoxicity on severity of acute renal failure and mortality.

Study	Year	Number of pts	Clinical Setting	Dialysis necessary	Mortality (in hemodialysed pts)
Joachimsson [6]	1989	5181	Patients with coronary by-pass	1,4%	57%
Andersson [7]	1993	2009	Patients with coronary by-pass	1,2%	44%
Levy [8]	1996	16.248	Different indications	1,1%	34%
Rialp [9]	1996	1087	Patients in intensive unit care	-	76%
McCullogh [5]	1997	3695	Cardiac catheterism	0,5%	37%
Chertow [10]	1997	43642	Patients with coronary by-pass	1,1%	63,7%
Gruberg [11]	2000	12054	Cardiac catheterism	0,4%	25,5%

(e.g. $< 1,5$ mg/dl). This may be the case frequently in elderly, malnourished patients, with low body mass. *In consequence, in any patient scheduled for an imagistic procedure requiring RCA administration, creatinine clearance calculation by Cockcroft-Gault formula or, better, by MDRD study formula is mandatory* (see Addenda). Also, one should note the fact that in more severe renal dysfunction, the amount of administered RCA leading to ARF is lower; thus, at creatinine clearances below $30 \text{ ml/min/1.73 m}^2$, even lower volumes of RCA, like 15-30 ml, may determine severe ARF, requiring hemodialysis [12].

Table 2 Risk factors for radiocontrast-induced nephropathy.

Chronic renal failure (creatinine clearance $< 60 \text{ ml/min/1.73 m}^2$)
Diabetes mellitus
Proteinuria (early stage nephropathy)
Severe arterial hypertension
Congestive cardiac failure
Dehydration
Large volumes of radiocontrast agents
Cholesterol embolism

To a lesser degree than chronic kidney disease, the presence of long-standing diabetes mellitus, of a renal disease without significant renal dysfunction (but with significant proteinuria), of severe arterial hypertension, cardiac failure or of dehydration/hypotension of any cause, are main causes of RCA-induced ARF. Some factors associated with invasive procedures may also promote RCIN: hypotension during the interventional procedure, cholesterol embolism, intraaortic contrapulsation, and the use of high volumes and concentrations of RCA [1]. Probably the most frequent under-estimated factor which contributes to acute renal dysfunction after cardiac catheterism is cholesterol embolism, often asymptomatic, but present in up to 50% of cases [13].

4 Pathogenic mechanism

Mechanisms involved in the pathogenesis of RCIN (Figure 1 and Table 3) are not entirely clear, but seem to involve complex pathogenic links. A detailed discussion of pathogenesis of RCIN is beyond the aims of this review – for a synthesis see Peerson *et al*, *Kidney International* 2005; Detrenis et al., *Nephrology Dialysis Transplantation* 2005) [14, 15]. Briefly, there is a determinant contribution of hemodynamic alterations, endothelial dysfunction, vasoactive mediators, rheologic factors, free oxygen radicals release, immunological mechanisms, direct tubular toxicity and other mechanisms. These pathogenic links underline different therapeutic strategies for prevention of RCIN presented below.

Table 3 The main pathogenic links involved in radiocontrast-induced nephropathy.

Pathogenic link	
Hemodynamic changes	RCA determines prolonged renal vasoconstriction (especially in medulla), adenosine-mediated → ↓ renal flux → ↓ glomerular filtration rate
Endothelial dysfunction	↓ κ B nuclear factor mediated NO synthesis → ischemic lesion, endothelin-mediated
Vasoactive substances	↑ intracellular calcium activation of the renin-angiotensin system prostaglandin inhibition atrial natriuretic peptide release (protective mechanism) ADH release (vasoconstriction)
Rheologic factors	↓ renal papilla capillary flux, ↓ erythrocyte sedimentation rate, ↑ erythrocyte aggregation → plasmatic hyperviscosity
Free oxygen radicals	Post ischemic reperfusion → oxygen reactive species release → endothelial dysfunction
Direct tubular toxicity	Membrane and cytoplasmic tubular proteins alteration → apoptosis
Immunological mechanisms	C3 activation ↑ polymorphonuclears and macrophages influx in the renal mesangium

5 Clinical features of radiocontrast-induced nephropathy

The most frequently used definition of RCIN is an increase of serum creatinine levels after RCA administration with more than 25% from baseline; alternatively, RCIN is defined as an increase with more than 0.5 mg/dl following radiocontrast exposure. In most cases, serum creatinine rises at 24 hours, reaching a peak at 48 to 96 hours after

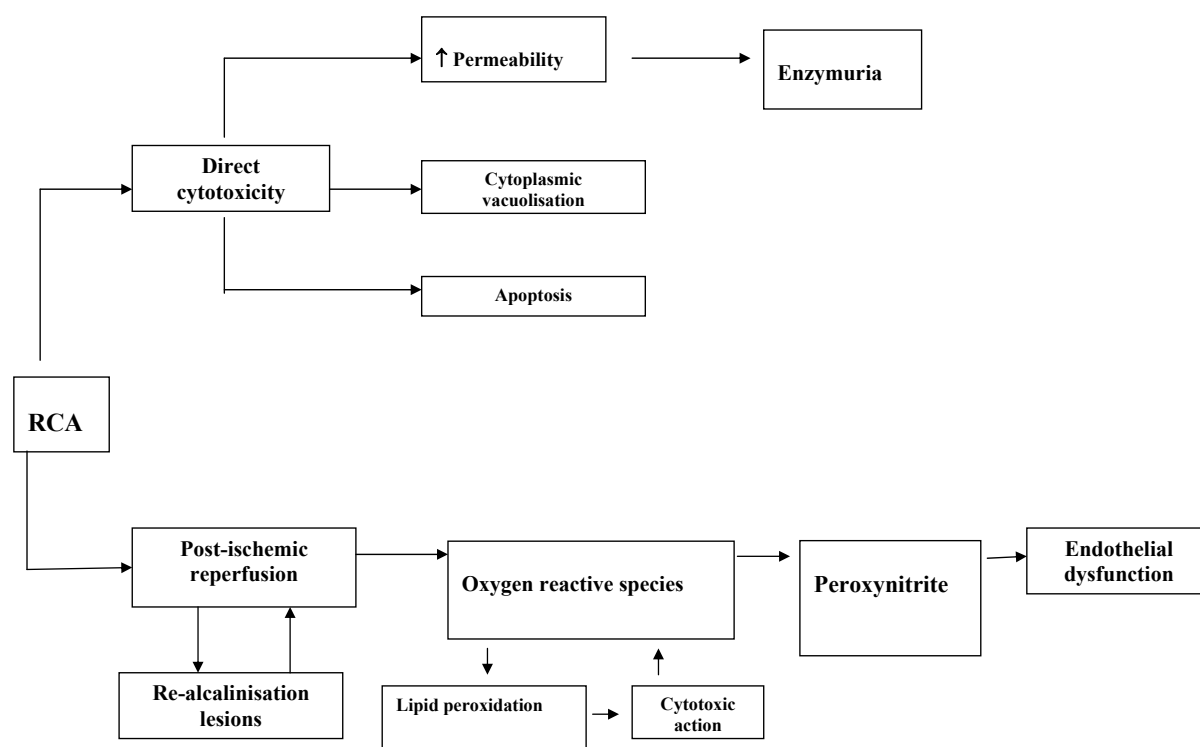


Fig. 1 Pathogenesis of radiocontrast-induced nephropathy. RCA = radiocontrast agent.

RCA exposure. Usually, serum creatinine levels fall to baseline levels in about 2 weeks after the initial renal aggression [8]. The exclusion of other causes of ARF is mandatory in defining RCIN [14]. For many clinicians, renal function decline represents a “benign creatininopathy”. Nevertheless, ARF is a serious complication, with a major impact on further mortality of patients exposed to RCA [1].

6 Radiocontrast agent type and the renal risk

The main types of RCA are outlined in Table 4. The data accumulated in recent years emphasise major differences between the various types of RCA in terms of physical and chemical properties, as well as the impact upon the renal function. Thus, non-ionic monomeric RCA, with reduced osmolarity, would be less nephrotoxic than the ionic ones or those with increased osmolarity, at least in the case of patients with renal dysfunction [16]. However, the widespread opinion claiming that the non-ionic hypo-osmolar RCA would be less nephrotoxic cannot, however, be firmly supported by Class A data in medical literature [15]. So far there are only few comparative studies with a small number of patients [17, 18]. The incidence of RCIN according to the type of RCA used is outlined in Table 5. These data [16, 18–26] should be taken with caution, considering the heterogeneity of the studies.

Theoretically, iso-osmolar RCA, compared to low-osmolarity RCA, may reduce intravascular resistance. In terms of rheology, this assumption is false. Osmolarity, accord-

Table 4 The main iodinated radiocontrast agents.

Class	Contrast agent
Ionic monomer, with high osmolality (1500-1800 mOsm/Kg)	Diatrizoate (Gastrografin ^R)
Ionic dimer, with low osmolality (600-850 mOsm/Kg)	ioxaglate (Hexabrix ^R)
Nonionic monomer, with low osmolality (600-850 mOsm/Kg)	iopamidol (Iopamiro ^R), iomeprol (Iomeron ^R), iopromid (Ultravist ^R), iohexol (Omnipaque ^R), iopentol (Imagopaque ^R)
Nonionic dimer, iso-osmolal (about 290 mOsm/Kg)	iodixanol (Visipaque ^R)

Table 5 Incidence of radiocontrast-induced nephropathy according to the use of different radiocontrast agents. S-Crea = Serum creatinine. NAC= N-Acetylcysteine.

Reference	RCA type	No of patients	RCIN incidence	Observations
Briguori, J Am Coll Cardiol 2002 [19]	Iopromid	183	11% 6% with NAC	Average S-Crea 1,5 mg/dl
Huber, Radiology 2002 [20]	Iopremol	100	16% 4% with theophylline	S-Crea $\geq 1,3$ mg, ≥ 100 ml RCA
Taliercio, J Am Coll Cardiol 1991 [21]	Iopamidol	307	8% 19% with diatrizoate	S-Crea $> 0,5$ mg/dl at 24 h
Kay, JAMA 2003 [22]		200	12% 4% with NAC	Patients with stable, moderate CRF
Oldemeyer, Am Heart J 2003 [23]		97	6,4% 8,2% with NAC	
Rudnick, Kidney Int 1995 [16]	Iohexol	1196	3% 7% with diatrizoate	RCIN defined as $\uparrow$ S-Crea ≥ 1 mg/dl/48-72 h S-Crea 1.5-3 mg/dl
Aspelin, N Engl J Med 2003 [18] Durham, Kidney Int 2002 [24]		129 diabetics 79	26% 22% 26,3% with NAC	
Aspelin, N Engl J Med 2003 [18] Boccalandro, Catheter Cardiovasc Interv 2003 [25]	Iodixanol	129 diabetics 279	S-Crea 1.5-3 mg/dl 12% 13% with NAC	
Baker, J Am Coll Cardiol 2003 [26]		80	21% 5% with NAC	

ing to Poisseuille's law, does not have any influence on blood flow, while blood viscosity is decisive [14]. The "modern", iso-osmolar, dimeric RCA (iodixanol, for example) are highly viscous compared to low-osmolality RCA. Warming up the dimeric RCA before perfusion might reduce viscosity.

7 Prevention of radiocontrast-induced nephropathy

7.1 Adequate hydration

Even in patients with normal renal function, hydration *during* the imagistic procedure is not enough to prevent RCIN. Bader *et al.* [27] administered to a group of patients 2000 ml of normal saline solution 12 hours before and after the procedure, while the control group received only 300 ml of serum during the procedure. In pre-hydrated patients, the reduction of the glomerular filtration rate was significantly less important (18 ml/min/1.73 m²) compared to subjects receiving minimal hydration (34.6 ml/min/1.73 m²). The incidence of RCA nephropathy defined in this investigation as an increase by at least 50% of serum creatinine from baseline, was of 5.3% in patients adequately hydrated, compared with 15% in the low-hydration. Notably, in this study a low-osmolar RCA was used [27].

Previously, it was believed that half-isotonic saline solution (0.45%) may be superior to isotonic solution (0.9%) in the prevention of contrast nephropathy. It has been advocated that the half-isotonic solution would have also the advantage of less sodium loading in patients with heart failure. Nevertheless, a prospective, randomised, controlled investigation [28] in 1620 patients showed that the incidence of RCIN was low (0.7%) in patients receiving isotonic saline, compared to subjects receiving half-isotonic solution (2% incidence, $p = 0.04$). The incidence of side effects was similar in the two groups. Both groups received a similar quantity of fluids (on average 430 ml before the intervention, 360 ml during angioplasty and 1270 ml after the coronary intervention) [28].

According to more recent data, hydration with *sodium bicarbonate* solution may be more efficient than normal saline administration. In a randomised study [29] in 119 patients with a serum creatinine level > 1.1 mg/dl, sodium bicarbonate (sodium load of 154 mEq/l) or normal saline (sodium load of 159 mEq/l) were infused before and after iopamidol administration. An increase by at least 25% of serum creatinine was noticed in 8 (13.6%) patients treated with saline and only in one patient (1.7%) treated with the sodium bicarbonate solution [29].

7.2 Diuretics

Although diuretics were largely used in the '90s, their efficiency in the prevention of RCIN has not been proved. Furthermore, there is clinical evidence discouraging the use of diuretics in this clinical setting. Solomon *et al.* [30] have shown in a prospective, randomised study in patients with high risk for RCIN, that the administration of furosemide or mannitol just before the angiographic procedure leads to a higher incidence of RCIN (28% in subjects receiving mannitol and 40% in patients treated with furosemide, compared to only 11% in patients receiving exclusively saline solution) [30]. These results are comprehensive taking into account the risk for hypovolemia associated with diuretic use.

7.3 N- Acetylcysteine (NAC)

The use of NAC, a drug with several biological actions, has recently become very popular in the prevention of RCIN. Although initially used as mucolytic agent, the discovery of its anti-oxidant properties led to its use in acetaminophen intoxication and in coronary heart disease. However, the exact mechanisms of action are incompletely understood: there might be either a direct antioxidant effect, or an effect mediated by the induction of glutathion synthesis triggered by NAC [31]. The use of NAC in various clinical settings is attractive due to low costs and a favourable side effects profile.

The clinical interest for NAC in the prevention of RCIN has increased after the publication of the data of Tepel *et al.* [32] from a prospective, randomised, placebo-controlled investigation in 83 subjects with mild-to-moderate renal dysfunction. Patients receiving NAC developed RCIN in only 2% of the cases, whereas in controls receiving placebo, the incidence of RCIN (defined as an increase in creatinine serum with at least 0.5 mg/dl in the next 48 hours after the administration of RCA) was 28%. In the group treated with NAC, serum creatinine decreased significantly (from 2.5 to 2.1 mg/dl, $p < 0.001$) within 48 hours, whereas in the placebo group there was an insignificant increase in serum creatinine levels (from 2.4 to 2.6 mg/dl, $p = 0.18$) [32]. Subsequent small-sized studies examining the potential role of NAC in RCIN prevention led to contrasting results.

Finally, Kshirsagar *et al.* [32] meta-analysed 16 studies published between 2000-2003, quite heterogeneous in number of patients, dosage (600-1500 mg/day) and the method of NAC administration. The results of the meta-analysis were rather disappointing: the nephroprotective role of NAC in patients with high risk for RCIN could not be established. The authors of the meta-analysis underline the need of a large scale research, randomised and placebo-controlled study designed to clarify the role of NAC administration in the prevention of RCIN [33]. Several studies in this respect are underway. We should also mention a recent randomised controlled investigation [34] in 295 patients in need of coronary bypass surgery that led to negative results. Consequently, according to the present data, NAC administration for the prevention of RCIN is still controversial; nevertheless, taking into consideration the low costs, the ease of administration and the rare side effects, N- Acetylcysteine may be still used (along with other more relevant measures) in the prevention of radiocontrast-induced nephropathy.

7.4 The adenosine antagonists (theophylline and aminophylline)

The use of aminophylline and theophylline as antagonists of adenosine is logical from a physiopathologic point of view; numerous experimental studies showed that the persistent vasoconstriction is in part mediated by adenosine. Theophylline and aminophylline are competitive antagonists of adenosine; these drugs were used in largely inhomogeneous trials regarding the moment of administration and the dosage of RCA. Moreover, these trials used various definitions of RCIN and included generally a small number of patients. A recent meta-analysis [35]. analysed all 7 randomised trials, involving 480 subjects,

which used theophylline in the prevention of RCIN. The subjects treated with theophylline had a decrease by 11.5% in serum creatinine ($p = 0.004$) compared to the control group. Only one patient treated with the adenosine antagonist needed acute hemodialysis for severe RCIN. The nephroprotective effect of adenosine antagonism proved to be, in this meta-analysis, independent from the type of study, the type or the amount of RCA, or the presence or absence of volume expansion [35].

7.5 Fenoldopam mesylate (FM)

FM is a specific agonist for the dopaminergic receptor 1; according to experimental data, FM is able to maintain the intrarenal blood flow unaltered after the administration of RCA. Some observational and small-sized randomised studies had to encouraging results [36]. In order to clarify the possible/potential favourable effect of fenoldopam administration, Stone *et al.* [37] conducted a prospective, placebo-controlled, double-blind study. The investigation included 315 patients with creatinine clearances <60 ml/min. The average age was 70 years, and the average creatinine clearance was 29 ml/min; about half of the investigated subjects were diabetics. The average amount of RCA was 157 ml. Patients randomised to the active treatment arm received, along with standard hydration, fenoldopam in a dosage of $0.05 \mu\text{g/kg/min}$ up to $0.10 \mu\text{g/kg/min}$; the placebo group was treated only with hydration according to standard protocols. The incidence of RCIN (defined as an increase of the serum creatinine with at least 25% in the first 96 hours post-intervention) was 33.6% in the fenoldopam arm, and 30.1% in the placebo group (not statistically significant). There were also no significant differences in 30-days mortality rates (2% versus 3.8%), the need for dialysis (2.6 versus 1.9%) or the re-hospitalisation rate (17.6 versus 19.9%) [37].

Two recent studies [38, 39] comparing fenoldopam with N-Acetylcysteine led to disappointing results regarding the therapeutic efficiency of the dopaminergic agonist: the administration of fenoldopam is less efficient than of NAC [38], or brings no supplementary advantages compared to NAC, a drug with easy administration [39]. Consequently, according to the current knowledge, fenoldopam is not efficient in the prevention of radiocontrast-induced nephropathy.

7.6 Extracorporeal treatments

To date, it is not clear if the *preventive* hemodialysis in high-risk patients (mainly with significant pre-existing renal dysfunction) may blunt the deterioration of renal function after exposure to RCA. Theoretically, even end-stage renal disease (ESRD) patients with significant residual diuresis may benefit from preventive hemodialysis just after the administration of the radiocontrast agent. Residual diuresis is essential for maintaining an adequate volume status and allows a more liberal fluid intake in ESRD patients. Moreover, residual diuresis contributes significantly, along with the chronic renal replacement therapy (chronic hemodialysis or peritoneal dialysis), to the removal of uremic toxins.

However, *preventive* hemodialysis is not efficient for the avoidance of radiocontrast-induced nephropathy both in ESRD and in non-ESRD patients [40–43]. The efficiency of substance removal by hemodialysis depends on various factors such as blood flow, dialysate flow, permeability of the dialysis membrane, duration of hemodialysis, size of the RCA molecule, binding capacity to plasma proteins, hydrophilia and electrical charge of the RCA. Moreover, in order to remove the RCA molecules, several hemodialysis sessions are generally necessary. Furthermore, the removal of RCA through peritoneal dialysis takes up to 3 weeks. Moreover, the hemodialysis session by itself may cause a reduction of renal function by triggering certain inflammatory reactions by releasing vasoactive substances leading to intradialytic hypotension. Repeated hypotensive episodes during dialysis may alter renal function or reduce residual renal function [44].

However, there is significant criticism to the opinion that extracorporeal treatments are not a valid option in preventing RCIN; indeed, the fact that the period between the administration of RCA and the start of the dialysis session was too long in some investigations is a serious argument [45] moreover, a “mild” hemodialysis session, with a blood flow of only 140 ml/min removes only a third of the RCA at most [46]. Schindler *et al* [45] have compared the efficiency of the various types of extracorporeal epuration on the elimination of RCA. These authors have demonstrated convincingly that “high-flux” hemodialysis and hemodiafiltration eliminate the RCA molecules significantly, whereas “low-flux” (conventional) hemodialysis has a modest effect on the removal of RCA.

A recent investigation [47] has demonstrated the high efficiency of hemofiltration, an extracorporeal procedure superior to hemodialysis in terms of hemodynamic stability, regarding RCIN prevention. Patients with high risk for RCIN (serum creatinine > 2 mg/dl) have been randomised either to hemofiltration (with a rate of fluid replacement >1000 ml/hour and without weight reduction) or to conventional hydration (for 4-8 hours pre-intervention and 18-24 hours after the RCA exposure). Acute hemodialysis for severe acute renal failure was necessary in 25% of patients treated by simple hydration and in only 3% of the patients treated prophylactically by hemofiltration (HF). The rate of significant in-hospital clinical events was 52% in the control group and only 9% in the HF group. Furthermore, in-hospital mortality was 2% in the group treated by HF (*versus* an alarming 14% in the control group). Finally, cumulative annual mortality was 10% with hemofiltration and 30% in patients treated conventionally [47]. Though the beneficial effect of HF in the prevention of RCA-induced renal toxicity is convincing, to date these data have a limited clinical application; hemofiltration is costly and technically demanding, and therefore prohibited for routine use in many clinical settings.

In conclusion, according to current knowledge, preventive hemodialysis in patients at high risks of RCIN is not a clear therapy option; however, intensive “high-flux” hemodialysis and hemodiafiltration are valid alternatives (already in use in many clinics) in patients at risk for RCIN. Prophylactic hemofiltration is a highly efficient but costly alternative.

7.7 Contrast agents containing gadolinium

Contrast agents using gadolinium for magnetic resonance imaging (MRI) are generally considered to lack significant nephrotoxic effects. However, for CT imaging, the gadolinium doses currently used are significantly higher. With these doses, the nephrotoxic effects of gadolinium become obvious; Erley and co-workers [48] have shown, in a randomised trial, that the nephrotoxic effect is similar with conventional iodinated RCA and with gadolinium-containing RCA.

7.8 Other prophylactic measures

Potentially nephrotoxic medication must be stopped, whenever possible, at least 1-2 days before the exposure to RCA. Potent nephrotoxic agents are aminoglycosides, vancomycin, amphotericine B and, noteworthy, non-steroidal anti-inflammatory drugs. NSAIDs, largely used in various clinical settings, may significantly reduce the glomerular filtration rate by interfering with intrarenal vascular autoregulation.

Table 6 Current strategies in the prevention of radiocontrast-induced nephropathy (according to evidence-based medicine).

Therapeutic strategy	Therapy indication class
<i>Hydration with normal saline</i>	I
Half-normal saline	IIb
Hydration with sodium bicarbonate solution	I
Diuretics (furosemide, mannitol)	III
Fenoldopam	III
Aminophylline/theophylline	IIa
N-acetylcysteine	IIb
Prophylactic conventional haemodialysis	III
“High-flux, high-efficiency”haemodialysis	I
Hemofiltration	I
Avoidance of potentially nephrotoxic drug	I

Therapy indication:

Class I: evidence or general acceptance of the utility and efficiency of the therapeutic procedure

Class II: Controversies about utility and efficiency of the therapeutic procedure

Class IIa: General opinion rather favorable to the procedure

Class IIb: General opinion rather unfavorable to the procedure.

Class III: Evidence or general acceptance of uselessness of a diagnostic or therapeutic procedure, which can even be harmful, in some situations.

8 Conclusions

Due to the large-scale use of radiocontrast agents (RCA) during imagistic procedures, radiocontrast-induced nephropathy (RCIN) is an important iatrogenic cause of acute renal failure. Mechanisms of RCIN production are complex, including direct tubular toxicity, tubular lesion induced by hypoperfusion and the increase of oxidative stress, as well as endothelial dysfunction. The most important risk factor for RCIN is pre-existent renal dysfunction; other important causes are hypovolemia, diabetes mellitus, the use of potentially nephrotoxic medication, and significant cardiac dysfunction. The RCA dose also seems to play an important role, but the relative “nephroprotection” by non-ionic low-osmolality radiocontrast agents is highly controversial.

To date, there are some certainties, and yet many controversies, concerning the prevention of RCIN. Adequate hydration with normal saline and/or sodium bicarbonate solution is certainly beneficial; withholding potentially nephrotoxic drugs is mandatory. Recent investigations have proven the beneficial effect of the administration of aminophylline/theophylline in the prevention of tubular renal toxicity induced by RCA. Preventive hemodialysis is controversial; certainly, conventional hemodialysis, by its reduced efficiency in removing the RCA, does not prevent RCIN. However, conventional hemodialysis may aggravate renal dysfunction by hemodynamic instability (especially in dehydrated patients, with heart failure or diabetes mellitus). “High-flux” hemodialysis and particularly hemofiltration efficiently prevent RCIN, but the widespread use of these modern techniques is limited for reasons of high-costs. Finally, the use of N-Acetylcysteine, though controversial, is recommended until the publication of clarifying Class A studies. Table VI shows a synthesis of various strategies for the prevention of RCIN, according to the principles of evidence-based medicine.

Addenda. Creatinine clearance calculation

Cockcroft-Gault formula

Creatinine clearance (ml/min/1.73m²) = [(140-age) × weight (kg) / 72 × serum creatinine (mg/dl)] (× 0.85 in women)

MDRD formula

Creatinine clearance (ml/min/1.73m²) = 186 × [serum creatinine (μmol/l) × 0.0113]^{-1.154} × age (years)^{-0.203} (× 0.742 in women)

Direct calculation of creatinine clearance

Creatinine clearance (ml/min/1.73m²) = urinary creatinine (mg/dl) × urinary volume (ml) / serum creatinine (mg/dl) × time of collection (minutes)

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