

## MISE AU POINT/IN-DEPTH REVIEW CONTRAST-INDUCED NEPHROPATHY

Salim N. KABALAN, Badiia G. EL-IMAD, Abdallah S. GEARA

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**RÉSUMÉ :** Avec les progrès de la radiologie interventionnelle, surtout en cardiologie, la néphropathie induite par produit de contraste (CIN) constitue la 3<sup>e</sup> cause d'insuffisance rénale. La pathogenèse de la CIN demeure controversée mais l'explication la plus plausible reste la combinaison de mécanismes vasoactifs entraînant une lésion cytotoxique direct de l'épithélium tubulaire. Plusieurs interventions ont été utilisées pour réduire l'incidence de la CIN. L'hydratation est l'intervention la plus approuvée bien que le meilleur protocole soit sujet à controverse : • L'hydratation avec le bicarbonate pendant sept heures donne les meilleurs résultats • N-acétylcystéine se révèle utile dans quelques catégories de patients à haut risque • L'hémofiltration réduit la mortalité à long terme chez les patients avec une créatinine de base  $\geq 4$  mg/dl • Le rôle bénéfique des inhibiteurs calciques demande des recherches plus approfondies. La meilleure façon de prévenir la CIN consiste à réduire chaque fois que possible l'utilisation des produits de contraste surtout chez les patients diabétiques et/ou insuffisants rénaux.

### INTRODUCTION

Contrast-induced nephropathy (CIN) was first described in 1955 by Alwall et al., and first discussed in the *New England Journal of Medicine* in 1968 [1]. CIN has generated since much interest for several reasons : first, the increasing use of contrast media (CM) in radiological and interventional procedures especially in cardiology. Second, CIN has become the third leading cause of acute renal failure in hospitalized patients with an incidence of 12% [2]. Third, with aging, the incidence of renal failure increases, which predisposes more to CIN. Finally, there were several papers published during the last years discussing several measures that could prevent the occurrence of CIN.

The renal failure typically occurs immediately after CM administration, peaks in the second or third day, and

usually the serum creatinine (sCr) returns to baseline value within 2 weeks [3]. CIN is nonoliguric in the vast majority of patients, oliguria is more common in patients with preexisting renal insufficiency and permanent renal failure may occur in up to 50% of these patients. Other distinct features of oliguric CIN include low urinary sodium and a fractional excretion of sodium  $< 1\%$  [4].

The critical value or the percentage of increase in sCr that defines CIN differs between the different studies, but the most widely used marker is an increase of  $> 25\%$  or  $> 0.5$  mg/dl above the baseline value of sCr within 48-72 h of CM administration [5].

Some have tried to diagnose CIN according to radiological findings : A nephrogram that persists 24 hours after contrast study is characteristic of CIN but not pathognomonic and a nephrogram is considered abnormal if the intensity on the films obtained 20 min after injecting contrast agent is equal or superior to that seen on the 5 min film [6].

The differential diagnosis of acute renal failure occurring after angiography involves distinguishing contrast nephropathy from renal atheroemboli. The latter has one or more of the following distinguishing characteristics : other embolic lesions or livedo reticularis, transient eosinophilia and hypocomplementemia, delayed onset of renal failure for days to weeks, protracted course with frequently little or no recovery of renal function [4].

### CONTRAST MEDIA

Contrast agents have evolved remarkably since their use was first considered in 1896, shortly after the description of X-rays by Roentgen. First attempts included sodium iodide, among many other both simple and complex compounds. Since then, several CM have appeared and disappeared in the market till currently only one non-ionic dimeric CM is commercially available in the USA and Europe, iodixanol, with decreased osmolality that has become close to that of blood (Table I) [7].

Much attention has been paid to reduce the osmolality of CM, but at the cost of viscosity. So iso-osmolal CMs are dimers and consequently have greater viscosity than monomeric low-osmolal CMs. This greater viscosity could explain the toxicity of these iso-osmolal CMs. More proximal tubular cell vacuolization, erythrocyte aggregation and cessation of blood flow to the medulla were observed with iso-osmolal compared to low-osmolal CMs. But these pathological findings did not correlate with the clinical course of CIN [8].

A decreased incidence of CIN appears to be associated

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Department of Internal Medicine, Rafik Hariri University Hospital (RHUH), Lebanese University, Beirut.

Address for correspondence or reprints requests : *Salim Kabalan, MD. RHUH. Beir Hassan - Beirut. Lebanon.*

Tel. : +961 1 830 000 / 3 84 88 40

Fax : 961 1 347 164 E-mail : kab@dm.net.lb

**TABLE I**  
**CONTRAST MEDIA : IONIC, OSMOLAL & MOLECULAR**  
**CHARACTERISTICS**

IONIC HIGH-OSMOLAL MONOMERS (1500 to 1800 mOsm/kg)	Diatrizoate : Renografin® Na-meglumine : Hypaque®
IONIC LOW-OSMOLAL DIMERS (600 to 850 mOsm/kg)	Ioxaglate : Hexabrix®
NONIONIC LOW-OSMOLAL MONOMERS (600 to 850 mOsm/kg)	Iopamidol : Solustrast®, Iopamiro® Niopam® Iomeprol : Iomeron® Ioversol : Opitray® Iopromide : Ultravist® Iohexol : Omnipaque® Iopentol
NONIONIC ISO-OSMOLAL DIMERS ( 290 mOsm/kg)	Iodixanol : Visipaque®

with nonionic agents which can be either low-osmolal (600-850 mOsm/kg) or iso-osmolal (290 mOsm/kg). Multiple studies have been performed to determine whether these newer agents afford a degree of protection against CIN great enough to justify their significant greater cost (3-5 folds).

Although it does appear that there are fewer hemodynamic and allergic complications with low-osmolal CM, studies have not confirmed that their use is uniformly associated with a decreased incidence of CIN [3]. Schwab's prospective study of 443 patients did not report any statistical difference in the incidence of CIN when comparing low-osmolality CM (8%) versus high-osmolality CM (10.2) [9]. Rudnick et al. found the same results as Schwab's study in nondiabetic patients with normal renal function (high-osmolality CM 8.2% versus low-osmolality CM 8.5%) [10]. However, even in the aforementioned studies, when patient groups were stratified, and patients with other risk factors were identified, there did appear to be some difference between high-osmolality and low-osmolality CM : benefit of low-osmolality (3%) CM versus high-osmolality (14%) only in patients with underlying renal insufficiency.

Compared with low-osmolal nonionic agents, iodixanol, the only currently available iso-osmolal nonionic CM, may lower incidence of CIN among diabetics with renal insufficiency. This statement was confirmed in Aspelin et al. prospective study, which showed : a lower peak in the sCr within the first three days (iodixanol 0.13% versus iohexol 0.55%), lower incidence of increase of sCr > 0.5 mg/dl (3% vs 26% respectively), lower incidence of increase of sCr > 1 mg/dl (0% vs 15%

respectively), lower mean change in sCr within the first week (0.07 vs 0.24) [11].

The primary benefits of nonionic CM, whether low or iso-osmolal, is seen in high-risk patients especially with sCr levels above 1.5 to 2 mg/dl and/or diabetics. For iso-osmolal versus low-osmolal nonionic CM, the benefit was among diabetics with renal insufficiency [10].

The volume of CM administered correlates with the risk of CIN : Rihal et al. found that each 100 ml of CM administered was associated with a significant increase of 12% in the risk of CIN [12]. It has been found that adjustment of the volume of CM to the patient's body weight and sCr level can minimize the risk of CIN. The recommended maximum volume of CM is [13] :

5 ml x body weight (kg)/serum creatinine level (mg/dl)

to a maximum dose of 300 ml.

However, diabetic patients with a sCr above 5 mg/dl may be at risk from as little as 20 to 30 ml of CM.

Rieger et al. found that gadolinium could be used as an alternative CM for diagnostic and interventional angiographic procedures in patients with impaired renal function. The use of gadolinium has sufficient radiographic density to allow adequate diagnostic visualization with less nephrotoxicity than iodinated CM [14]. In the same context, The European Society of Urogenital Radiology recommended against the use of gadolinium-based CM in patients with renal impairment, reasoning that they are more nephrotoxic than iodinated CM in equivalent X-ray attenuating doses.

R. Solomon et al. in a review published recently [15] and focusing on the route of administration, the manner of X-ray attenuation, and the specific chemical structure of the CM concluded that the single available iso-osmolality CM is associated with a low rate of CIN even in high risk patients.

Carbon dioxide (CO<sub>2</sub>), which has no nephrotoxicity, has been considered as an alternative contrast agent. However, in most cases of angiographies and in particular interventions, CO<sub>2</sub> as a sole contrast agent has not been consistently reliable. CO<sub>2</sub> was used in Rieger's study as an additional contrast agent in conjunction with gadopentetate dimeglumine to reduce the amount of contrast agent used.

## RISK FACTORS

Prospective studies have found that a small rise in the sCr (averaging 0.2 mg/dl) is a common occurrence after a radiocontrast study. A more marked decline in renal function occurs in patients with one or more of the following risk factors (Table II).

### Underlying renal insufficiency

Underlying renal insufficiency with sCr level exceeding 1.5 mg/dl or glomerular filtration rate (GFR) being less than 60 ml/min per 1.73 m<sup>2</sup> : the incidence followed an exponential increase starting from a baseline sCr > 1.2 mg/dl

**TABLE II**  
RISK FACTORS FOR CONTRAST NEPHROPATHY

<b>Established risk factors</b>	
Preexisting renal insufficiency	
Diabetes mellitus	
Volume of contrast	
Intravascular volume depletion	
<b>Possible risk factors</b>	
Congestive heart failure	
Recurrent contrast procedures	
Multiple myeloma	
Hypercalcemia	
Proteinuria	
Hyperuricemia	
Use of concomitant nephrotoxic medications	
Atherosclerotic vascular disease	
Hypertension	

[16]. In patients with sCr > 5 mg/dl the risk of requiring dialysis and permanent renal failure increases.

#### Diabetes mellitus

Diabetes type I patients are more predisposed to CIN than patients with diabetes mellitus type II. Although patients with diabetes and normal renal function should be evaluated carefully, most appear to be at fairly low risk for developing CIN [17]. However, patients with diabetes mellitus and preexisting renal insufficiency represent a group with an extremely high risk of developing CIN. In addition, clinical and experimental studies suggest that hyperglycemia increases the risk of CIN due to the increased susceptibility to renal ischemia [18-19].

**TABLE III**  
RISK ASSESSMENT FOR PREDICTING CIN  
AFTER PERCUTANEOUS CORONARY INTERVENTION

<b>Risk factors</b>	<b>Integer score</b>
Hypotension	5
Use of intra-aortic balloon pump	5
Congestive heart failure	5
Serum creatinine > 1.5 mg/dl	4
Age > 75 years	4
Anemia	3
Diabetes mellitus	3
Volume of contrast media	1 per 100 ml used
<b>Risk categories</b>	<b>Total score</b>
Low	< 6
Moderate	6-10
High	11-15
Very high	> 15

#### Others

Etiologies that cause reduced renal perfusion (e.g. hypovolemia, advanced heart failure), multiple myeloma : mostly due to volume depletion in myeloma patients and interaction between light chains and contrast agent [20], multiple contrast studies within a 72 hours period, age of the patient, male gender.

#### Risk stratification

Mehran et al. developed a simple scoring method that integrates 8 baseline clinical variables to assess the risk of CIN. The incidence was 7.5% among patients with a low score and 57.3% among those with a high risk score (Table III) [21].

#### PATHOGENESIS

The mechanism by which CIN occurs is not well understood. The two major theories, based largely upon studies in experimental animals, are renal vasoconstriction and direct toxic effect of the CM.

#### Renal vasoconstriction (Fig. 1)

The renal medulla is a particular vulnerable kidney region : it is an area of high energy requirements that is maintained on the verge of hypoxia where the pO<sub>2</sub> can be as low as 20 mmHg [22].

The injection of CM induces early, rapid renal vasodilation followed by prolonged vasoconstriction, with an increase in intrarenal vascular resistances, so there is a reduction of the total renal blood flow and a decrease in GFR. It was suggested that the marked diuresis secondary to CM will activate the tubulo-glomerular feedback (TGF), with a secondary vasoconstriction of the glomerular afferent arterioles, therefore resulting in decrease in the GFR and an increase in renal vascular resistance by almost 50% [5].

Since the urinary concentration of adenosine increases after CM administration and this increase seems to be directly related to CM osmolality, it is possible that adenosine contributes to the pathogenesis of CIN mediated through the A1 receptor induced vasoconstriction [26]. The administration of CM in large volumes increases plasma and urine levels of endothelins and this seems unrelated to the osmolality of CM. The interaction between adenosine and endothelins as mediators of renal hemodynamic is not yet well defined. It has been hypothesized that the diuresis and natriuresis induced by endothelins play a role in determining increases in renal tissue-related values of adenosine. Prostaglandins (PG) PGE1 and PGE2 are able to inhibit endothelin transcription implicated in vasoconstriction mechanisms. PGE1 in particular seems to have a direct cytoprotective effect.

The calcium ion has a very important role in both TGF and the myogenic response of the afferent arterioles. The increase in intracellular calcium provokes vasoconstriction in intrarenal circulation [23].

Atrial natriuretic peptide (ANP) has different protec-

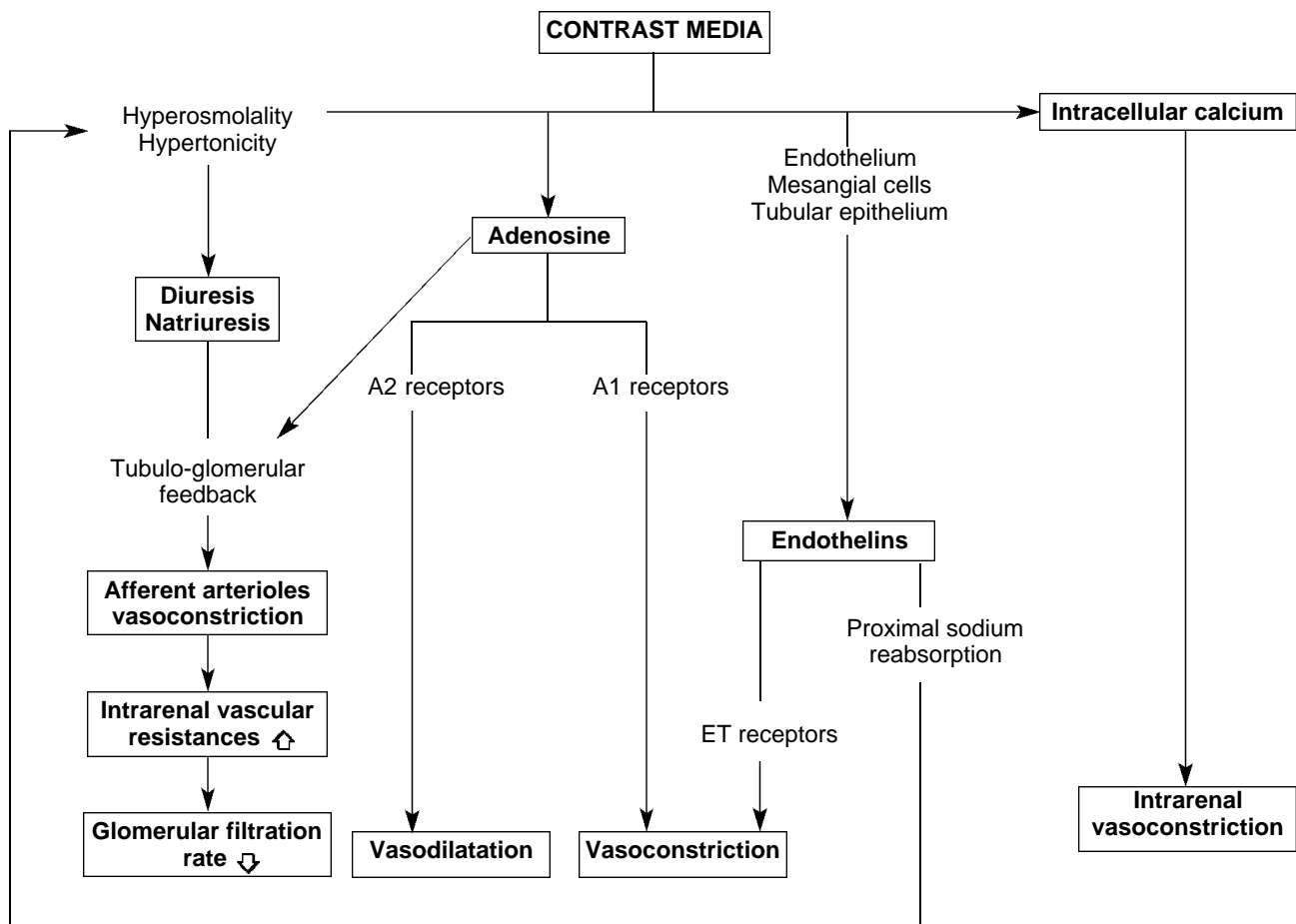


FIGURE 1. Vasoconstrictive effect of contrast media.

tive roles in CIN : it increases hydrostatic pressure and GFR, dilates the afferent arterioles and vasoconstricts the efferent arterioles, blocks tubular sodium reabsorption, induces redistribution of the renal medullary flow, inhibits endothelin-induced vasoconstriction and offers resistance to the TGF. In addition, vasoconstriction induced by antidiuretic hormone (ADH) can increase CM-induced ischemia [24].

#### Direct tubular toxicity (Fig. 2)

There is some experimental evidence that endothelial dysfunction is partly due to oxygen free-radicals generation during post-ischemic reperfusion. Free oxygen radicals, particularly superoxide anion, react with nitric oxide to produce peroxynitrite, an oxidative and very reactive nitro active species capable of further reducing the bioavailability of nitric oxide, thereby increasing tissue damage. It is also responsible of nitrosation of tyrosine residues of enzymes, such as prostacycline synthase and nitric oxide synthase, which are involved in the synthesis of medulla vasodilators [25].

The hypertonicity and hyperosmolality of CM reduce the volume and deformability of the erythrocyte membrane, contributing to an increase in blood viscosity and

the worsening of selective medullary hypoperfusion [26].

Furthermore, within two hours of CM administration, diffuse or focal cytoplasmic vacuolization has been reported, with lysosomal alterations in the proximal convoluted tubule cells and the internal cortex. This vacuolization seems reversible, with tendency to resolve within a few days [26].

#### Other mechanisms

It has been confirmed that in vitro CM precipitates the Tamm Horsfall protein, which is the major physiological constituent of the urinary casts. Experiment in rats 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 the alternative pathway by direct stimulation of endothelial cells. This mechanism is of questionable clinical consequence. CM also stimulates the influx of polymorphonucleates and macrophages in the mesangium : therefore, the pathogenesis of CIN could 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 GFR [26].

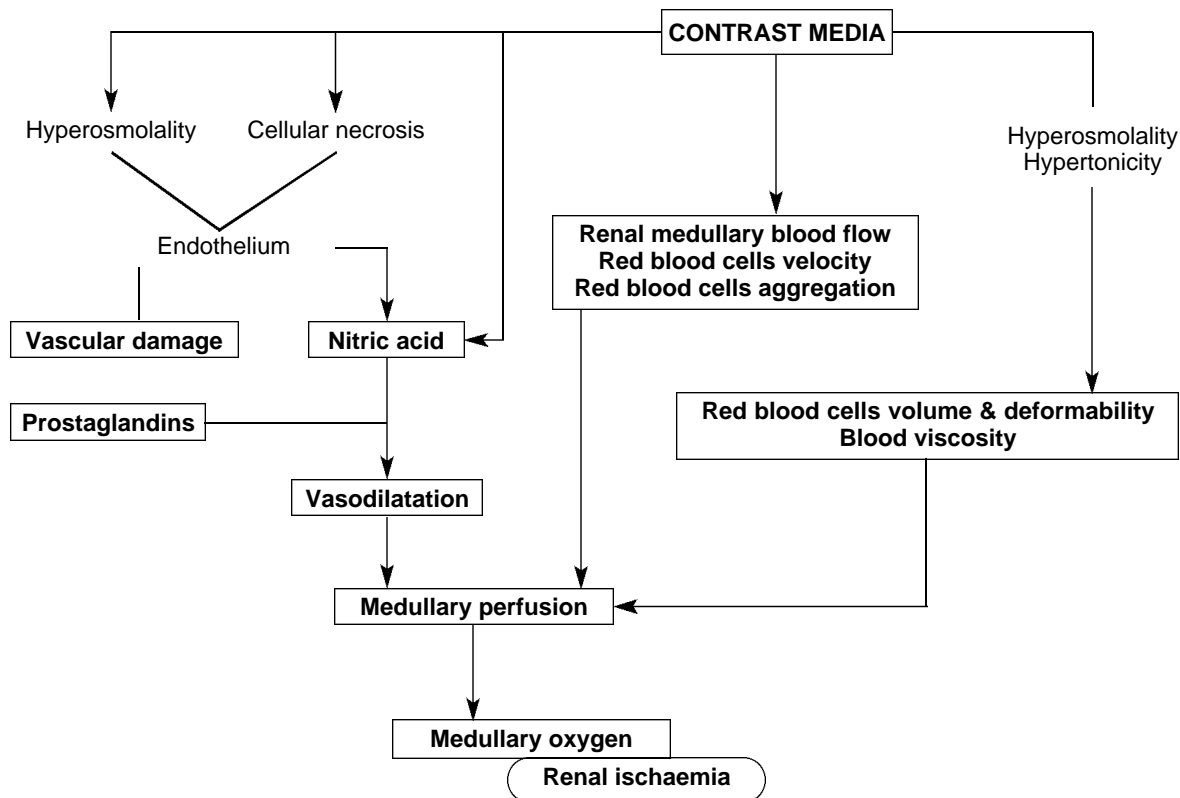


FIGURE 2. Direct cytotoxic effect of contrast media.

## PREVENTION

The best treatment of CIN is prevention. Some preventive measures include [4, 27-28] :

- The use, if clinically possible, of ultrasonography, magnetic resonance imaging or CT scanning without radio contrast agents, particularly in high-risk patients.
- The use of lower doses of CM and avoidance of repetitive studies that are closely spaced : repeated exposure should be delayed for 48 hours in those without risk factors, and for 72 hours in those with diabetes mellitus or pre-existing renal dysfunction.
- If CIN develops, repeated exposure should be delayed until the patient's sCr has returned to its baseline.
  - Avoidance of volume depletion.
  - Non steroidal anti-inflammatory drugs (NSAIDs), diuretics (when feasible), dipyridamole and possibly angiotensin converting enzyme inhibitors (ACEI) should be discontinued 1-2 days before administration of CM.
  - The use of the smallest possible amount of nonionic, hypo-osmolal or iso-osmolal CM in patients at risk.

## Hydration

The optimal hydration solution to help prevent CIN is unclear (Table IV). Some evidence suggest that hydration with isotonic saline may be superior to one-

half normal saline. The benefit with isotonic saline was more pronounced in diabetics (0% versus 5.5%) and those given more than 250 ml of contrast (0% versus 3%) [32].

Hydration with sodium bicarbonate may be more effective in preventing CIN. In a prospective study involving 119 patients, the incidence of CIN was significantly lower in those administered sodium bicarbonate (154 meq/l) (3 ml/kg/h as a bolus for 1 hour prior to contrast administration, followed by a 1 ml/kg/h for 6 hours post-procedure) versus the group of patients which had the same regimen hydration with normal saline (1.7% vs 13.6% respectively). These results suggest that the infusion of isotonic sodium bicarbonate should be the intravenous hydration solution of choice. It has the additional advantage of a shorter pretest regimen than the other saline regimens [33].

A few small trials have also evaluated the effectiveness of oral hydration or an outpatient hydration protocol. In the PREPARED study, there was no difference in the maximal change in plasma creatinine between the group who received oral hydration and those who received parenteral hydration half normal saline [31].

## N-acetylcysteine

This drug is inexpensive, well tolerated and devoided of significant side effects. It reduces renal damage by scavenging oxygen free radicals, generated as a result of

**TABLE IV**  
EFFECTIVENESS OF SALINE HYDRATION OR FORCED DIURESIS, OR BOTH,  
IN PREVENTING CIN REPORTED IN CLINICAL TRIALS

TRIAL	Patients Number	Baseline Cr mg/dl	Intervention	Rate of CIN (%)	Superior	Comments
SOLOMON et al. [29]	78	2.1	• 1/2 NSS <sup>a</sup> 12 h before & after • 25 g mannitol 1 h before • 80 mg furosemide 1/2 h before	11 28 40	Saline hydration (p = 0.02)	<i>CIN was lower with saline compared to previously reported incidence</i>
PRINCE [30]	98	2.6 2.3 2.7	• 1/2 NSS 150 ml/h • Furosemide 1 mg/kg + dopa <sup>b</sup> + mannitol 12.5g • Furosemide + dopa	31 32 34	None*	<i>High urine output was associated with lower rate of CIN**</i>
PREPARED [31]	36	1.4	• 1/2 NSS (75 ml/h) 12 h before & after • Oral hydration (1000 ml/10h) + 1/2 NSS 6 h before	After 48 h 0.21 After 48 h 0.12	None	
MUELLER et al. [32]	1620	0.9 (0.5-1.6)	• D5 1/2 NSS • NSS 0.9%	1 2	Isotonic saline (p = 0.04)	<i>Especially in women, diabetic, CM &gt;150 ml</i>
MERTEN et al. [33]	119	1.1	• NaCl 154 meq/l • NaHCO <sub>3</sub> 315,4 meq/l	13.6 1.7	Sodium bicarbonate (p = 0.02)	<i>7 h hydration protocol</i>

<sup>a</sup> NSS : normal saline 0.9%    <sup>b</sup> dopa<sup>3</sup> : dopamine 3 µg/kg/min

\*Forced diuresis with IV crystalloid, furosemide, mannitol and low-dose dopamine provides a modest benefit against CIN provided a high urine flow can be achieved.

\*\*Maintenance of urine output >150 ml/h can prevent CIN.

toxic damage to renal tubules. N-acetylcysteine may also have direct vasodilating effects on the kidneys through an increase in the biological effects of nitric oxide, which is a potent and stable vasodilator contributing to improved renal hemodynamics [34]. Different trials have studied the effect of N-acetylcysteine in the prevention of CIN with controversial results (Tables V, VI) :

A meta-analysis of the first 7 reported trials showed that, compared with peri-procedural hydration alone, administration of N-acetylcysteine plus hydration reduced the risk of CIN by 56% among patients with chronic renal insufficiency [46]. The authors of two other metanalysis stated that it was impossible to draw general conclusions about the benefit of N-acetylcysteine in preventing CIN because of inconsistent study designs of the analyzed trials [47-48].

A systematic review showed that studies reporting negative results for N-acetylcysteine had enrolled patients at lower overall risk of CIN compared with studies reporting positive results (incidence of nephropathy 11% and 24.8% respectively). Therefore, N-acetylcysteine may be of benefit mostly in high-risk patients. A meta-analysis showed an overall benefit of the drug, but only in patients with more severe renal dysfunction (sCr level > 2.5 mg/dl) or when a nonstandard or incomplete hydration protocol were used [49].

In patients undergoing emergency diagnostic procedures, in which a full hydration protocol is not possible,

an abbreviated hydration regimen plus oral or intravenous administration of N-acetylcysteine was successful in reducing the rate of CIN [50-51]. In another study, a double dose of N-acetylcysteine plus intravenous saline hydration administered before and after angiography in patients with chronic renal insufficiency significantly reduced the incidence of CIN compared with a single dose of N-acetylcysteine [52].

An intriguing difference between the studies is their geographic location : American studies were negative. The formulation of N-acetylcysteine in the USA is usually a liquid for oral administration. In Germany, the drug is distributed in a solid form, as a tablet. In Taiwan, the drug is distributed as solid granules. In addition, in US studies the drug was generally added to ginger ale, orange juice, or other beverages to help mask the flavor. It is conceivable that these may have changed the chemical nature of the drug [49].

### Hemofiltration

Hemofiltration did provide significant benefits related to short-term and long-term survival. The greatest long-term benefit was observed in patients with higher baseline sCr > 4 mg/dl. Until additional data are available, consideration should be given to the use of hemofiltration among patients at the highest risk to CIN (i.e. diabetics with a baseline sCr > 4 mg/dl) [53].

### Other preventive measures

**Adenosine antagonists** : The administration of theophylline does not provide any additional benefit over hydration alone, especially in patients with preexisting renal impairment. The use of adenosine antagonists may be beneficial only in patients where sufficient hydration may be impossible or in patients with a concomitant decrease in renal blood flow (e.g. congestive heart failure) [8].

**Calcium-channel blockers (CCBs)** : Acute administration of CCB before the procedure is not enough to prevent CIN. Only one randomized controlled study supports a beneficial effect of CCB for the prevention of CIN. In that study, patients in the control group did exhibit some decline in renal function [8].

**Fenoldopam** : The benefit of fenoldopam was not validated in a large multicentric randomized placebo-controlled double-blind trial. A definitive conclusion regarding the drug's ability to protect against CIN could not be reached.

**Mannitol, furosemide, endothelin1 antagonists, low dose dopamine and ANP** were found to have a negative effect in the prevention of CIN [54].

*L-arginine, ascorbic acid, PGE1 and ACEI* beneficial effects should be studied further.

### MANAGEMENT OF CIN

Today, no specific therapy has been found to be of benefit. ANP was tried as a treatment for CIN but did not demonstrate an overall reduction in the need for dialysis. Dopamine was tried by Abizaid et al. but proved to be detrimental with higher sCr peak and higher rate of dialysis [55].

### CONCLUSION

CIN is a common cause of iatrogenic acute renal failure. Primary prevention of CIN is the most effective way of decreasing its incidence. Assessing the patient's risk, selecting a procedure most appropriate for the patients are the most important steps. Patients with risk factors for CIN requiring contrast study should first be optimized by attempting to correct any risk factor. In patients whose risk factors could not be corrected or reversed, care should be taken in choosing the type and

**TABLE V**  
SUMMARY OF PROSPECTIVE STUDIES OF NAC VERSUS PLACEBO FOR PREVENTION OF CIN  
IN WHICH BENEFICIAL EFFECTS WERE SHOWN

STUDY	Patients Number	NAC dose	Procedure	Baseline sCr mg/dl	Definition of CIN	Rate of CIN/ Odds ratio
DIAZ-SANDOVAL et al. [35]	54	600 mg bid (1 before, 3 after)*	Coronary angiography	1.6 (0.045)	> 25%	NAC : 8% Placebo : 45% p = 0.005 <b>0.21 (0.06-0.80)</b>
KAY et al. [36]	200	600 mg bid for 48 h*	Coronary angiography ± Plasty	1.4 (0.44)	> 25%	NAC : 4% Placebo : 12% p = 0.03 <b>0.32 (0.10-0.96)</b>
SHYU et al. [37]	121	400 mg bid for 48 h	Coronary angioplasty	2.8 (0.8)	0.5 mg/dl	NAC : 3% Placebo : 25% p < 0.001 <b>0.13 (0.08-0.20)</b>
TEPEL et al. [38]	83	600 mg bid for 48 h	CT scanning	2.4 (1.3)	0.5 mg/dl	NAC : 2% Placebo : 21% p = 0.01 <b>0.10 (0.02-0.90)</b>
MINER et al. [39]	180	2000 mg bid for 2-3 doses	Coronary angiography or plasty	1.5 (0.37)	25%	NAC : 2% Placebo : 21% p = 0.04 <b>0.37 (0.14-0.93)</b>
MACNEIL et al. [40]	43	600 mg bid for 48 h*	Coronary angiography	1.6 (0.4)	25%	NAC : 5% Placebo : 32% p = 0.046 <b>0.11 (0.101-0.99)</b>

\*24-hour hydration protocol not used    **bid** : twice daily

**TABLE VI**  
SUMMARY OF PROSPECTIVE STUDIES OF NAC VERSUS PLACEBO FOR PREVENTION OF CIN  
IN WHICH BENEFICIAL EFFECTS WERE NOT SHOWN\*

STUDY	Patients Number	NAC dose	Procedure	Baseline sCr mg/dl	Definition of CIN	Rate of CIN/ Odds ratio
BOCCALANDRO et al. [41]	179	600 mg bid for 48 h	Coronary angiography ± Plasty	1.8 (0.6)	0.5 mg/dl	NAC : 13% Placebo : 12% <b>1.14 (0.43-2.98)</b>
DURHAM et al. [42]	79	1200 mg 1 h before & 3 h after	Coronary angiography	2.2 (0.4)	0.5 mg/dl	NAC : 5% Placebo : 32% <b>1.27 (0.4-4.03)</b>
BRIGUORI et al. [43]	183	600 mg bid for 48 h	Coronary or peripheral angiography ± Plasty	1.5 (0.4)	25%	NAC : 5% Placebo : 32% <b>0.95 (0.61-1.48)</b>
ALLAQUABAND et al. [44] <sup>a</sup>	123	600 mg bid for 48 h	Coronary angiography ± Plasty	2 (0.6)	0.5 mg/dl	NAC : 5% Placebo : 32% <b>1.23 (0.34-4.51)</b>
GOLENBERG et al. [45] <sup>b</sup>	80	600 mg tid for 48 h	Coronary angiography ± Plasty	2 (0.38)	0.5 mg/dl	NAC : 5% Placebo : 32% <b>1.30 (0.27-6.21)</b>

\* All patients received 24h saline hydration protocol.  
<sup>a</sup> One group of patients was randomly assigned to receive fenoldopam plus hydration.  
<sup>b</sup> Beneficial effect was observed only in patients with baseline serum creatinine 2.5mg/dl.

bid : twice daily  
tid : three times/day

the amount of CM.

All patients undergoing contrast studies should have their renal function checked : sCr should not be older than 6 months. If the patient has known abnormal sCr level at the time of referral or will undergo procedures requiring intra-arterial CM administration, the serum creatinine should be measured within 7 days of the examination. sCr should be rechecked two to three days after the procedure.

Although there are many new promising modalities in the prevention of CIN, hydration is still the most effective method of prevention.

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