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The Toxicity of Iodinated Radiographic Contrast Agents in the Clinical Practice

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Abstract

Iodinated radiographic contrast agents (IRCA) are pharmaceutical agents used to improve the visibility of internal organs and structures in X-ray based imaging techniques. However, IRCA may have adverse unwanted effects, ranging from a mild inconvenience, such as itching, to a life-threatening emergency. The adverse effects of IRCA include delayed allergic reactions, anaphylactic reactions, and/or cutaneous reactions. But exposure to IRCA may be associated also with the development of either hyperthyroidism or hypothyroidism, presumably due to the effect of free, biologically active elemental iodine ions present in these agents. Among the side effects associated with the use of intravascular injection of IRCA, Contrast-induced nephropathy (CIN) is undoubtedly their most important and frequent well known adverse reaction. The pathogenesis of CIN is discussed in detail including the factors that increase the incidence of CIN, the main ones being pre-existing renal impairment, particularly when associated with diabetes mellitus. Finally, the measures to reduce the nephrotoxicity of IRCA are suggested beginning with monitoring renal function, discontinuation of potentially nephrotoxic drugs, use of either iodixanol or iopamidol at the lowest dosage possible. The main procedure for prevention of CIN is an adequate hydration of the patient with either isotonic sodium chloride or sodium bicarbonate solutions. A long list of references is provided that will enable readers a deep appreciation of the topic.

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Introduction

Iodinated radiographic contrast agents (IRCA) are commonly administered pharmaceutical agents very useful for improving the visibility of internal organs and structures (Iodine is an important element used in contrast media because it possesses high-contrast density) in X-ray based imaging techniques, such as radiography, angiography and contrast-enhanced computed tomography (CT) scans, and to perform cardiac catheterizations and percutaneous coronary interventions. They have been in use for over 60 years and their use for imaging and intravascular intervention keeps increasing, particularly in less healthy and older patients, with one or more comorbid conditions, such as advanced vascular disease, severe long-standing hypertension, diabetes and impairment of renal function **[1]**.

All currently used X-ray contrast media are based on the tri-iodinated benzene ring, acetrizoate being the parent tri-iodinated contrast medium first in clinical use **[2]**.

Side effects of iodinated radiographic contrast agents (IRCA)

We know that any pharmaceutical agent, in addition to having a useful effect, may also be responsible for side effects that may be minor and acceptable or severe and even dangerous. As IRCA have no therapeutic effects, the ideal agent should be able to provide optimal imaging quality without substantial adverse reactions at the same time **[3]**. But IRCA, in addition to their common usefulness for diagnostics in clinical practice, may have adverse unwanted effects, ranging from a mild inconvenience, such as itching, to a life-threatening emergency **[4]**. With the advent of non-ionic, low-osmolality contrast media (LOCM) in the 1980s most adverse events are relatively mild and require no medical treatment **[5]**

Among the side effects associated with the use of intravenous or intra-arterial injection of IRCA, Contrast-induced nephropathy (CIN) is undoubtedly their most important and frequent well known adverse reaction. Other forms of adverse effects include delayed allergic reactions, anaphylactic reactions, and/or cutaneous reactions **[6]**.

Previous allergic reactions to contrast material increase the risk of developing future adverse reactions to IRCA. In order to decrease the chance of allergic side effects, including anaphylaxis or a life-threatening emergency, pre-treatment of patients who have such risk factors with a corticosteroid and diphenhydramine has been suggested: either Prednisone (50 mg orally, 13, 7, and 1 hour before contrast injection), or Hydrocortisone (200 mg intravenously, 1 hour before contrast injection), or Methylprednisone (32 mg orally, 12 and 2 hours before contrast media injection); Diphenhydramine (50 mg intravenously/ intramuscularly/ orally 1 h before contrast injection) **[7]**.

Among the unwanted effects of IRCA, we have to mention hypersensitivity reactions. These may be: (a) mild, with an incidence <3%, consisting of immediate skin rashes, flushing or urticaria; (b) moderate to severe, with an incidence <0.04%, including angioedema, coronary artery spasm, hypotension, cardiac failure and loss of consciousness. Asthma, a history of multiple allergies and therapy with beta blockers increase the risk of bronchospasm. Mortality is less than one death per 100,000 patients.

As soon as a reaction occurs, the intravascular infusion of the contrast media must be ceased and treatment with antihistamine started. Bronchospasm and wheezing, laryngospasm and stridor or hypotension should be treated immediately with adrenaline, intravenous fluids and oxygen, in addition to antihistamines with or without hydrocortisone **[8]**.

Other side effects of IRCA are the so-called 'Delayed adverse reactions' that are usually cutaneous (with an incidence reported from 1% to 23%) and include rash, skin redness, and skin swelling, sometimes associated with nausea, vomiting and dizziness; they begin 1 hour or longer (usually 6 to12 hours) after the administration of the contrast agent and are usually mild and non–life threatening (sometimes can be moderate to severe) and usually not brought to the attention of the radiologist and ascribed to other causes **[9]**. Since patients are usually discharged from the radiology department within half an hour of contrast administration, these reactions are rarely observed by the radiologist. 'Delayed adverse reactions' are significantly ($p<0.05$) more frequent with dimeric nonionic agents (16.4%) than with a monomeric nonionic agents (9.7%) **[10]**. They vary in size and presentation, but are usually pruritic and self-limited; symptoms can be treated with corticosteroid creams. The pathophysiology of delayed cutaneous reactions is speculative, but likely represents a spectrum of T cell–mediated delayed hypersensitivity **[6]**.

Previously, we have documented that both a single and/or a multidrug treatment, in particular clinical conditions, may be related to a higher development of adverse drug reactions (ADRs) and/or drug-drug interactions (DDIs) **[11-16]**, and this represents a major issue during the clinical management of any disease requiring polytherapy. The same mechanisms involved in ADRs are determinant for adverse side effects observed after iodinated radiographic contrast agents.

Contrast-Induced Thyroid Dysfunction

There has been little examination of the effect of IRCA on thyroid function in the scientific/medical literature.

Exposure to IRCA may be associated with development of either hyperthyroidism or hypothyroidism. This is presumably due to the effect of free, biologically active elemental iodine ions present in

the IRCA. It has been suggested that long storage and exposure to light of IRCA leads to photolytic degradation of contrast media, causing increase concentration of free elemental iodine in solution **[17]**.

The terms iodine and iodide are often used interchangeably. Iodide refers to the metabolically important, non-organic free form that can be present in excess. A 200 ml dose of an IRCA containing 35 µg/mL iodine provides 7,000 µg free iodine, equivalent to 45 times the recommended daily intake **[18]**. The dose of IRCA used in typical radiological procedure of medical practice contains approximately 13,500 µg of free iodide **[18]** and 15 to 60g of bound iodine **[3, 18]** that may be liberated as free iodide in the body **[19]**. This represents an acute iodide load of ninety to several hundred thousand times the recommended daily intake of iodide (150 µg) **[20]**.

Normally, the thyroid gland can regulate hormone synthesis and secretion in the presence of excessive amounts of iodine in the body. Iodine overload is accompanied by an autoregulatory phenomenon that inhibits thyroid hormone synthesis and release (Wolff–Chaikoff effect) **[21].** This effect is usually transient and lasts 8–10 days **[22]**. After several days of exposure to high iodine levels, an 'escape phenomenon' occurs from the acute Wolf-Chaikoff effect, which is mediated by downregulation of the sodium iodide transporter (NIS) that transports iodine into the thyroid; thus, normal thyroid hormone production resumes **[23, 24].** Failure of the acute Wolff-Chaikoff effect results in iodine-induced hyperthyroidism, or the Jod-Basedow phenomenon. Failure to escape from the acute Wolff-Chaikoff effect results in iodine-induced hypothyroidism **[25, 26]**.

Iodine-induced thyrotoxicosis after IRCA injection has been found in 7 of 28 cases of hyperthyroidism seen at a geriatric hospital **[27]**. Several studies have demonstrated the occurrence of hyperthyroidism following nonionic contrast radiography **[28]**.

Hintze et al **[29]** have investigated the occurrence of iodine-induced thyrotoxicosis in unselected patients from an iodine-deficient geographic area undergoing coronary angiography. Thyroid hormone values and urinary iodine excretion were determined before, and 1, 4 and 12 weeks after IRCA injection. Two of 788 unselected patients developed hyperthyroidism within 12 weeks; both patients had normal TSH levels at baseline and ultrasound of the thyroid was without evidence of nodules. The Authors concluded that in euthyroid unselected patients from an iodine-deficient geographic area short-term iodine contamination by contrast media rarely leads to hyperthyroidism.

Patients with pre-existing hyperthyroidism may develop a thyroid crisis. Patients with Graves' disease and multinodular goitre, especially elderly patients and patients living in areas of iodine deficiency, are at increased risk of developing thyrotoxicosis and should

receive iodinated contrast media only with close monitoring **[8, 18]**.

Patients with Hashimoto's thyroiditis or other autoimmune thyroid disease and patients, who have undergone partial thyroidectomy, are at risk for the development of iodine-induced hypothyroidism **[24]**.

Gartner and Weissel **[30]** have investigated the short-term effects of high doses of iodine (300–1221 mg of iodine per kilogram b.w.) on thyroid parameters in euthyroid patients. They measured serum concentrations of free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin (TSH) before and daily for 1 week after parenteral application of x-ray dyes (for coronary angiography or CT). TSH values increased significantly 3–5 days after the iodine load within the normal range with the exception of 4 patients (18%) who had a TSH increase above normal. FT4 and FT3 remained unchanged and there was no significant correlation between the dose of iodine and the TSH reaction. The Authors conclude that, even in euthyroid patients, the injection of IRCA, at the iodine dose ranging from 300 to 1221 mg of iodine per kilogram, can induce subclinical hypothyroidism.

Rhee et al **[26]** have performed a nested case-control study to assess the association between the exposure to IRCA and incident thyroid dysfunction, using a database of patients receiving care at Brigham and Women's Hospital and at Massachusetts General Hospital in Boston, MA (USA). Incident hyperthyroidism was defined as a thyrotropin level, at follow-up, below the normal range, and incident hypothyroidism as a thyrotropin level above the normal range; incident overt hyperthyroidism was defined as a follow-up thyrotropin level $\leq$0.1 mIU/L and incident overt hypothyroidism as a follow-up thyrotropin level >10 mIU/L, based on evidence that such levels are associated with cardiovascular morbidity and mortality and are less likely to be due to non-thyroidal illness. They found a significant association between IRCA exposure and subsequent development of incident hyperthyroidism, incident overt hyperthyroidism, and incident overt hypothyroidism; no association was found between IRCA exposure and incident hypothyroidism.

With widespread use of radiocontrast-enhanced imaging examinations, it is important for clinicians and radiologists to be aware of thyroid-specific complications **[24]**.

Iodine-induced hyperthyroidism is often difficult to treat, whereas iodine-induced hypothyroidism usually is self-limiting and resolves spontaneously **[24]**.

The iodinated radiographic contrast agents (IRCA)

IRCA have different osmolalities and different viscosities (Table). The ionic High-Osmolar Contrast Media (HOCM, e.g. diatrizoate) have an osmolality between 1500 and 1800 mOsm/kg, 5 to 8 times the osmolality of plasma. Nonionic Low-Osmolar Contrast Media (LOCM e.g. iohexol) have an osmolality between 600 and 850 mOsm/kg, 2–3 times the osmolality of

Table - Iodinated Contrast Media Commonly Used in Clinical Practice

Name	*Type*	*Iodine content (mg/mL)*	*Osmolality mOsm/kg*	*Osmolality type*	*Viscosity cps at 37°C*
Ionic					
Diatrizoate (Hypaque 50)	Monomer	300	1,550	HOCM	10.5
Metrizoate Isopaque (Conray 370)	Monomer	370	2,100	HOCM	3,4
Ioxaglate (Hexabrix)	Dimer	320	580	LOCM	7.5
Nonionic					
Iopamidol (Isovist-370)	Monomer	370	796	LOCM	9.4
Iohexol (Omnipaque 350)	Monomer	350	884	LOCM	10.4
Iodixanol (Visipaque 320)	Dimer	320	290	IOCM	11.8

The osmolality of contrast media is compared with the osmolality of plasma.
HOCM = High Osmotic Contrast Media have the highest osmolality, i.e. 5–8 times the osmolality of plasma.
LOCM = Low Osmotic Contrast Media have an osmolality still higher than plasma, i.e. 2–3 times the osmolality of plasma.
IOCM = Iso Osmotic Contrast Media have the same osmolality as plasma.
Cps: Viscosity in Centipoise.
*(Reproduced from **[75]** with permission)*
Data of viscosity from **[202].**

plasma. Nonionic Iso-Osmolar Contrast Media (IOCM e.g. iodixanol) have an osmolality of 290-300 mOsm/kg, the same osmolality as plasma **[6, 7, 31]**.

HOCM have greater cytotoxic effects on proximal tubular cells *in vitro* than do LOCM or IOCM. At equal iodine concentrations (300 mg I/mL), the HOCM ioxithalamate showed stronger cytotoxic effects than did other IRCA **[32]**. The use of LOCM rather than HOCM is beneficial in reducing the incidence of nephrotoxicity in patients with pre-existing renal failure **[33-36]**. Thus, the HOCM are used less frequently. There is no difference in the cytotoxicity of LOCM iomeprol and IOCM iodixanol at equal iodine concentrations in renal proximal tubular cells *in vitro* **[37]**. Recent studies and meta-analyses have shown no significant difference in the incidence of nephrotoxicity between IOCM and LOCM **[37-40]** with the exception of LOCM iohexol that is more nephrotoxic **[33, 41]**.

IRCA also have different viscosities (Table). The low osmolality achieved with the IOCM has been obtained at the price of increased viscosity; at comparable iodine concentrations and x-ray attenuation, the non-ionic dimeric IOCM have about twice the viscosity of non-ionic monomeric LOCM **[42-44]**.

Contrast-Induced Nephropathy (CIN)

The most important adverse unwanted effect of IRCA is undoubtedly the Contrast-Induced Nephropathy (CIN) also known as Contrast-Induced Acute Kidney Injury (CI-AKI). This is an Acute Renal Failure (ARF) occurring 24-72 hours after the exposure to

intravascular injection of IRCA that cannot be attributed to other causes **[45]**.

It is usually a nonoliguric ARF with asymptomatic transient decline in renal function, peaking on the third to fifth day, and returning to baseline within 10–14 days **[46]**. It is mirrored by an absolute (0.5 mg/dl or greater) or relative (by 25% or greater) increase in serum creatinine (SCr) from baseline or, better, by a decrease (to 30-60 mL/min - renal insufficiency – or less) in the estimated glomerular filtration rate (eGFR), i.e. the creatinine clearance calculated using the MDRD (Modification of Diet in Renal Disease) calculation **[47]** or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation **[48]**, or the very simple Cockcroft-Gault formula **[49]**. The Schwartz formula **[50]**, a creatinine-based prediction of GFR, depending on age, sex, body weight and serum creatinine can be useful for children: GFR = K(Height, cm)/SCr (mg/dL) (K=0.33 in premature infants; K=0.45 in term infants to 1 year old; K=0.55 in children to 13 years and adolescent females; K=0.65 in adolescent males).

In some cases, CIN may cause a severe impairment of renal function with oliguria (<400 mL/24 hrs), requiring dialysis. In these cases the mortality is high. The clinical feature and the management of CIN are the same as that for ARF due to other causes **[51-53].**

CIN occurs in approximately 5% of hospitalized patients who exhibit normal renal function prior to the injection of IRCA **[54]** and in about 2% **[1]** or even 1% of outpatients with eGFR >45 ml/min per 1.73 m^2 **[55]**.

Thus, CIN is uncommon in patients with normal pre-existing renal function. It occurs more frequently in patients with renal impairment, particularly if associated with diabetes mellitus **[56]**. Among all procedures utilizing IRCA for either diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary interventions are associated with the highest rates of CIN **[57]**. This occurs because of intra-arterial injection, since IRCA seem to be more nephrotoxic when given intra-arterially because of the higher acute intrarenal concentration **[58, 59]**, particularly if the arterial injection is suprarenal **[60-66],** and a high dosage of IRCA used; and also the type of patients who are usually in advanced age, with one or more comorbid conditions (e.g. advanced vascular disease, severe long-standing hypertension, diabetes and some renal function impairment) **[67]**.

Bruce et al **[68]** have performed a retrospective study on 11,588 patients undergoing CT either without IRCA (control group) or with the LOCM iohexol. They observed that the incidence of CIN in the iohexol group was similar to that of the control group up to a SCr level of 1.8 mg/dL; but when SCr was above 1.8 mg/dL the incidence of CIN was higher in the iohexol group.

Davenport et al **[69]**, in another retrospective study, found that i.v. low-osmolality IRCA is a risk factor for nephrotoxicity in patients undergoing CT with a

stable eGFR <30 mL/min/1.73 m^2; no nephrotoxicity was observed in patients with a pre-CT eGFR >45 mL/ min/1.73 m^2. The Authors concluded that i.v. IRCA is a nephrotoxic risk factor, but not in patients with a stable SCr <1.5 mg/dL or eGFR >45 mL/min/1.73 m^2.

Pathogenesis of CIN

The pathophysiological mechanisms responsible for CIN have not been fully elucidated yet **[70]**.

When IRCA are injected intravenously or intra-arterially, they immediately cause a hemodynamic renal biphasic response: there is an early, rapid renal vasodilatation with an initial increase in renal blood flow (RBF) that is followed by a more prolonged vasoconstriction with an increase in intrarenal vascular resistances and a reduction in total RBF **[71]**. The extrarenal vessels show transient vasoconstriction, followed by a stable decrease in vascular peripheral resistances **[72, 73]**. Then IRCA pass from the vascular compartment through glomerular capillaries into the Bowman space by glomerular filtration, and are concentrated in the renal tubular lumen by water tubular reabsorption. Their high concentration in the urine allows the visualization of the urinary tract. The fall in RBF causes decrease in glomerular filtration rate (GFR).

The result of these hemodynamic changes will be a renal ischemia, that is particularly marked in the renal medulla for an anatomical reason: the outer renal medulla, in fact, is distant from the descending *vasa recta* **[72, 73]**. Oxygen (O_2) delivery to the outer renal medulla is therefore poor, even under normal physiological conditions; in contrast with the limited regional O_2 supply, there is a high local O_2 consumption due to the important active tubular reabsorption in S3 segment of renal proximal tubules and in the medullary thick ascending limb of Henle's loops that are here located. But medullary hypoxia is made more severe by any increase in renal tubular reabsorption that implies an increase in O_2 consumption. In normal conditions prostaglandins, nitric oxide (NO), and adenosine continuously adjust medullary tubular transport activity to the limited available O_2 supply, by enhancing the regional blood flow and downregulating the tubular transport **[74]**. Defects in one or more of these protective mechanisms will cause medullary hypoxia. Since IRCA induce an osmotic diuresis and consequently an increase in tubular reabsorption in the Henle's loops due to increase of tubular fluid delivery, the consequent increased energy need and the higher O_2 consumption of the ascending limbs will worsen the already hypoxic environment in the renal medulla **[75, 76]**.

Sendeski et al **[77]** have isolated specimens of outer medullary descending *vasa recta* from rats and have microperfused them intraluminally with a buffered solution containing iodixanol, with an iodine concentration of 23 mg/mL to simulate the usual dosage for radiological procedures in humans. They demonstrated that iodixanol directly constricts the descending vasa recta (they caused 52% reduction of

their luminal diameter) by reducing NO and significantly increases the vasoconstrictor response to angiotensin II, thereby causing severe local hypoxia. Thus iodixanol, in doses typically used for coronary interventions, constricts medullary descending *vasa recta*, thereby causing severe medullary hypoxia.

Medullary hypoxia may lead to the formation of reactive oxygen species (ROS) **[78, 79]** that (a) may exert direct tubular and vascular endothelial injury, (b) may intensify renal parenchymal hypoxia by virtue of endothelial dysfunction and dysregulation of tubular transport **[80, 81]**, (c) may decrease NO synthesis that is believed to be due to its reaction with ROS, in particular superoxide anions ($O_2^{\cdot -}$) **[17, 82]**, leading to the formation of the more powerful oxidant peroxynitrite anion ($ONOO^-$) **[83].** Sendeski et al **[77]** have demonstrated that the superoxide dismutase mimetic Tempol reduced iodixanol-induced vasoconstriction, thereby supporting the role of ROS. More recently Pisani et al. **[84]** have demonstrated that a recombinant manganese superoxide dismutase, administered *in vivo* to rats undergoing diatrizoate treatment, was able to reduce renal oxidative stress, thereby preventing the reduction of GFR and the renal histologic damage that follows IRCA administration.

Patients with chronic renal failure (CRF) have defective antioxidant systems **[85]** and increased oxidative stress associated with inflammation and endothelial dysfunction **[86]**. This may explain why pre-existing renal failure certainly represents the most common condition predisposing to the development of CIN.

Thus, animal and human studies have clearly demonstrated that ROS generation is enhanced following IRCA administration, suggesting their important role in the pathogenesis of CIN **[82]**.

IRCA possess a cytotoxicity, that has been suggested to be due, at least in part, to the free iodine present in solutions of IRCA and that leads to apoptosis and cell death of both endothelial and tubular cells **[17]**.

The decrease in NO in the *vasa recta* may not be totally accounted for by increased ROS production; the damaged endothelial cells (including apoptosis) may be another important factor in decreasing NO; the decrease in NO production in the descending *vasa recta*, in fact, is partly due to a loss of endothelial cell viability caused by IRCA **[17]**. On the other hand, the endothelial cells are the first to come in contact with intravenously-injected IRCA. The endothelial damage, represented by nuclear protrusion, cell shrinkage, fenestration of the endothelial layer and formation of microvilli ('blebbing') on the cell membrane, and cellular apoptosis have been observed by scanning electron microscopy **[87]**. Endothelial damage may also release endothelin that causes vasoconstriction. Heyman et al **[88]** have in fact demonstrated that i.v. administration of contrast media in rats induced an increase in plasma concentration of endothelin and that IRCA stimulated endothelin release

from cultured bovine endothelial cells. Reduced levels of prostaglandins have also been suggested to predispose to CIN **[74]**.

IRCA cause a direct damage also on the epithelial renal tubular cells **[89]**. Once filtered by the glomeruli and concentrated in the renal tubules because of water reabsorption, in fact, they exert a direct injury to the renal tubular cells. The damage caused has been observed in isolated tubular segments and in cultured cells substantiated by disruption of cell integrity and apoptosis. This damage may be aggravated by factors, such as tissue hypoperfusion and hypoxia caused by IRCA and by clinically unfavourable conditions, such as pre-existing renal impairment particularly secondary to diabetic nephropathy, salt depletion and dehydration, congestive heart failure and concurrent use of nephrotoxic drugs **[17, 32, 75, 90]**.

The biochemical changes underlying the epithelial damage have been extended to study changes in major intracellular signalling pathways involved in cell survival, death and inflammation **[79, 91-98]** *in vitro* in cultured renal tubular cells **[99]**.

Recent studies have clarified these aspects in primary human tubular cells as well as in HK-2 cells exposed to different contrast media. Andreucci et al **[96]** demonstrated a decreased cell viability, secondary to a reduced activation of Akt/PKB and of ERK 1/2, both kinases known to play a pivotal role in cell survival/ proliferation, which was substantially alleviated by transfecting the HK-2 cells with a constitutively active form of Akt. The same Authors have demonstrated, in HK-2 cells, that contrast media affect the activation/ deactivation of transcription factors, like FoxO3a and STAT3, that control the genes involved in apoptosis and cell proliferation **[95, 97]**.

Studies in animals and *in vitro* studies suggest that IRCA can directly induce caspase-mediated apoptosis of renal tubular cells. Contrast-induced apoptosis may also be due to the activation of shock proteins and the concurrent inhibition of cytoprotective enzymes and prostaglandins **[100, 101]**.

Under physiological conditions, the Na^+/Ca^{2+} exchanger (NCX) can pump the Ca^{2+} outside the renal tubular epithelial cells using the Na^+ concentration gradient across the cell membrane to keep a low intracellular Ca^{2+} level. After IRCA injection, NCX may reversely extrude Na^+ for Ca^{2+} influx and result in intracellular Ca^{2+} overload that is considered to be an important factor in the pathogenesis of CIN **[102, 103]**.

At comparable iodine concentrations and x-ray attenuation, the non-ionic dimeric IRCA have about twice the viscosity of non-ionic monomeric IRCA **[42-44]**. The concentration of the IRCA within the tubular lumen increases considerably because of tubular fluid reabsorption. The result will be a progressive increase in tubular fluid osmolality and, due to the exponential concentration-viscosity relationship, an overproportional increase in tubular fluid viscosity **[44, 70]**. Since the

fluid flow rate through a tube increases with the pressure gradient and decreases with the flow resistance and since the resistance increases proportionally to fluid viscosity, the increased viscosity caused by IRCA increases the intratubular pressure **[44]**. Thus, the osmotic diuresis caused by IRCA raises the intratubular pressure with a condition of tubular obstruction that contributes both to the tubular epithelial damage and to the fall of GFR **[70]**.

The effect of IRCA on morphology of erythrocytes has been also studied **[104, 105]**. The formation of echinocytes and stomatocytes observed upon incubation of erythrocytes with IRCA may have a negative effect on the rheology of the blood **[17]**. IRCA affect the membrane skeleton of erythrocytes, with iopromide causing drastic changes in the band3-spectrin network compared with iodixanol that may contribute to microcirculatory disorders (especially in patients with coronary artery disease) and gas transport, contributing to tissue hypo-oxygenation **[106]**.

Factors predisposing to CIN

According to the European Society of Urogenital Radiology, patient conditions favoring CIN are represented by pre-existing renal impairment, particularly when associated with diabetes mellitus, salt depletion and dehydration, congestive heart failure, an age greater than 70 years and concurrent use of nephrotoxic drugs **[107]**.

Dehydration and salt depletion deserve a special discussion. Dehydration is the decrease of body water, as it occurs sometimes in old patients due to impaired sensation of thirst **[108]**. But the term dehydration is frequently used to indicate salt and water depletion. Dehydration and salt depletion are responsible for the reduction of the 'effective' circulating blood volume, i.e. the relative fullness of the arterial tree as determined by cardiac output, peripheral vascular resistance and total blood volume **[51]**.

The most important risk factor for the development of CIN is undoubtedly the presence of renal insufficiency, irrespective of its cause. The lower the eGFR, the greater is the risk of CIN following the administration of IRCA. Mehran and Nikolski **[57]** suggest an eGFR of 60 ml/min/1.73m^2 as a reliable cut-off point for identifying patients at high risk for CIN; the incidence of CIN in patients with CRF ranges from 14.8 to 55%. We have to mention, however, that recently Neyra et al **[109]**, in a retrospective observational in-hospital study on 1160 patients with or without chronic kidney disease, have observed that CIN occurred with similar frequency, following coronary angiography, in both patients with and without chronic kidney disease (eGFR ≥ 60 mL/min/1.73 m^2).

Another important condition favoring the development of CIN is diabetes mellitus, particularly when associated with renal insufficiency **[110]**.

Toprak et al **[111]** studied 421 patients with chronic kidney disease undergoing coronary angiography; 137 had diabetes mellitus, 140 had pre-diabetes and 144 had a normal fasting glucose; CIN occurred in 20% (RR = 3.6), 11% (RR = 2.1), and 5.5% respectively. A serum glucose concentration above 124 mg/dl was the best cut-off point for prediction of CIN after IRCA.

Schoolwerth et al **[112]** have observed that in diabetic patients with normal renal function the incidence of CIN is comparable to that of a nondiabetic population. But Hardiek et al **[113]** evaluated 122 diabetic patients with a SCr of ≤2 mg/dL in a double-blind randomized study using iopamidol-370 or iodixanol -320 for coronary angiography; 17 patients (10 iopamidol vs 7 iodixanol; p=NS) had an increase in SCr ≥25% over baseline; they concluded that diabetic patients with normal or mild renal dysfunction are at risk for CIN.

IRCA increase the release of renal adenosine, a vasoconstrictive agent, and stimulate renal adenosine receptors. The renal vasculature of patients with diabetes mellitus has a high sensitivity to adenosine. This may in part explain the particular susceptibility of diabetic patients to IRCA **[114]**.

Khamaisi et al **[115]** have underlined the important role of endothelins, produced by proteolysis of the precursor prepro-endothelins under the action of endothelin-converting enzyme, in causing renal vasoconstriction by IRCA; thus, the administration of IRCA to diabetics acutely reduces renal parenchymal oxygenation, a reduction that is most prominent in the renal medulla, since it already functions at low oxygen tension. Given that diabetics already have increased circulating and renal endothelin levels, this also may in part explain the particular susceptibility of diabetic patients to IRCA.

According to Mehran and Nikolski **[57]** the incidence of CIN in diabetic patients varies from 5.7 to 29.4%; at any given degree of baseline GFR, diabetes doubles the risk of developing CIN compared with nondiabetic patients. Most Authors do not regard the presence of diabetes mellitus in the absence of renal failure as a risk factor for CIN **[116]**.

Morabito et al **[117]** carried out a prospective observational study in 585 unselected patients who underwent elective or emergency coronary angiography or PCI; they observed a 5.1% incidence of CIN in diabetic patients with preserved renal function; this incidence was comparable to that of a nondiabetic population.

The concomitant use of nephrotoxic drugs such as aminoglycosides, cyclosporin A, amphotericin, cisplatin and nonsteroidal anti-inflammatory drugs is another

condition favoring CIN **[118, 119]**. Concerning nonsteroidal anti-inflammatory drugs, the reduction in the synthesis of the endogenous vasodilator prostaglandins (as occurring following the use of nonsteroidal anti-inflammatory drugs) will increase the nephrotoxicity of IRCA.

Hypercholesterolemia has been shown to impair endothelium-dependent vasorelaxation, which could make the kidney vulnerable to IRCA by inducing disorders in intrarenal prostaglandins and renal NO system, leading to the suggestion for use of statins as a protective measure against CIN.

Thus, Yang et al **[120]** carried out a study in rats to see whether hypercholesterolemia is a risk factor for IRCA toxicity. Rats were fed either a normal rodent diet or high-cholesterol diet; at the end of 2 and 8 weeks, 8 rats from each diet group were given a tail vein injection of either iohexol or vehicle. IRCA administration increased SCr and induced severe renal tubular necrosis in rats fed the high-cholesterol diet for 8 weeks, but not in rats fed the normal diet or high-cholesterol diet for only 2 weeks. The Authors concluded that long-term hypercholesterolemia is a risk factor for CIN, which might be associated with disorders in intrarenal prostaglandins and abnormalities in the renal NO system.

Angiotensin II is a main effector peptide in the renin-angiotensin system and plays a very important role in controlling renal homeostasis as a vasoconstrictor. But the role of renin-angiotensin-aldosterone system blocking agents, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in the pathophysiology of CIN, remains controversial **[110]**.

CIN was described for the first time in a patient with multiple myeloma receiving intravenous pyelography. Nowadays it is believed that the incidence of CIN in patients with multiple myeloma with a normal SCr is low and correlates with β_2-microglobulin levels; thus, the administration of contrast agents in these patients is relatively safe **[75, 121]**.

Other conditions favouring CIN include: prolonged hypotension, severe dehydration, reduction of 'effective' intravascular volume due to congestive heart failure, liver cirrhosis, or salt depletion secondary to abnormal fluid losses associated with insufficient salt intake, use of large doses of IRCA and their multiple injections within 72 hrs, route of administration (intravenous administration of IRCA are less risky than intra-arterial injection), osmolality and viscosity of contrast media, advance age (>65 years), anemia, sepsis and renal transplantation **[75].**

Measures for prevention of CIN

The first general rule when using IRCA for diagnostics or therapeutic procedures is that any patient should have his renal function measured before and after the procedure; in patients at high risk of CIN, SCr

and eGFR should be monitored before and once daily for 5 days after the radiographic procedure **[59, 122]**.

The second measure is that potentially nephrotoxic drugs (like aminoglycosides, vancomycin, amphotericin B, metformin and nonsteroidal anti-inflammatory drugs) should be discontinued before the IRCA injection **[122]**.

The third measure is the choice of the least nephrotoxic radiocontrast agent. Iodixanol (IOCM) and iopamidol (LOCM) appear to be the IRCA of choice to reduce risk of CIN **[123]**.

The fourth precaution is to use the lowest dosage possible of IRCA. Before the advent of CT, IRCA were administered mainly for urography and angiography procedures. In the pre-CT era, most radiologists were utilizing 30–50 ml HOCM with hand injection rates of less than 1 ml/s for urography. The average IRCA dose for CT is approximately 100–150 ml with power injection rates of up to 3–4 ml/s **[3]**

High doses of IRCA are actually required in coronary angiography and percutaneous coronary intervention. For these procedures, some formulas have been suggested to calculate the least dangerous dosage:

(A) Cigarroa's formula: 5 mL of IRCA/kg b.w./SCr (mg/dL). The maximum dose acceptable is 300 mL for diagnostic coronary arteriography **[124]**.

(B) Laskey's formula: volume of IRCA to calculated creatinine clearance ratio with a cut-off point of the ratio at 3.7 **[125]**; a cut-off point of the ratio at 2.0 is better: below a ratio of 2.0, CIN would be a rare complication; but it would increase dramatically at a ratio of 3.0 **[123, 126]**.

(C) Ratio of grams of iodine to the calculated creatinine clearance; a ratio of 1.42, or even better a ratio of 1.0, would prevent CIN **[123]**.

The fifth and very important measure to prevent CIN is an adequate hydration of the patient **[122, 127, 128]**. The old suggestion to limit fluid intake starting the day before contrast administration must be abolished. On the contrary, we have to give the patient a volume supplementation: e.g. 500 mL of water orally before and 2,500 mL for 24 hours after IRCA administration to secure a urine output of at least 1 mL/ min **[107]**. In high-risk patients the oral water load may be replaced by i.v. infusion of 0.9% saline at a rate of approximately 1 mL/kg b.w./hour, beginning 6–12 hours before and continuing for up to 12–24 hours after the radiographic examination (if urine output is appropriate and cardiovascular condition allows it) **[59, 127]**. The purpose is to cause expansion of intravascular volume, to suppress renin-angiotensin cascade and consequently to reduce renal vasoconstriction and hypoperfusion. Furthermore, the resulting increase of urine output will limit the duration of IRCA contact with renal tubules and consequently its direct toxicity on renal tubular epithelium **[129, 130]**.

Some Authors have stated a preference for using sodium bicarbonate hydration that has been shown to be superior to sodium chloride in clinical studies and meta-analysis **[131-139]**: for coronary angiography or intervention 154-mEq/L infusion of sodium bicarbonate as a bolus of 3 mL/kg b.w./hour for 1 hour before the administration of IRCA, followed by 1 mL/kg/hour for 6 hours during and after the procedure has been used **[132]**. The reason for using bicarbonate is the alkalinization of tubular fluid by bicarbonate that will reduce the production and increase the neutralization of oxygen free radicals, thereby protecting the kidney from injury by IRCA **[134, 135, 140, 141]**. Others did not find any benefit with sodium bicarbonate hydration versus sodium chloride **[142-145]** or have even found an increased incidence of CIN **[146]**. More recently, Brar et al **[147]** have stated the left ventricular end-diastolic pressure-guided fluid administration to be safe and effective in preventing CIN in patients undergoing cardiac catheterization. The European Renal Best Practice **[148]** position "recommends volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no volume expansion, in patients at increased risk for CIN" **[148]**.

We have mentioned that ROS may play an important role in the pathogenesis of CIN. Thus, antioxidants have been used to prevent CIN. The first antioxidant used for this purpose was N-acetylcysteine **[149].**

Short-duration pretreatment with N-acetylcysteine has been shown to reduce IRCA-induced cytotoxicity in human embryonic kidney cells treated with the ionic HOCM ioxithalamate, non-ionic LOCM iopromide and the IOCM iodixanol **[150]** and to ameliorate the ischemic renal failure in animal models **[151]**. The suggested dosage is 600 mg orally twice daily, the day before and the day of procedure **[59]** or, in patients unable to take the drug orally, an i.v. dose of 150 mg/kg over half an hour before the procedure or 50 mg/kg administered over 4 hours **[152]**.

But the protective effect of N-acetylcysteine against CIN in high risk patients is still controversial. Some studies have reported a protective effect **[152-154]**, others have denied it **[146, 155-161].**

Conflicting results have been obtained with the use of another antioxidant, ascorbic acid **[150, 162-166]**. The suggested dosage is 3 g orally 2 hours before the procedure and 2 g during the night and in the morning after the procedure **[162, 163]**.

Jo et al **[165]** have found that N-acetylcysteine at a dose of 1,200 mg orally twice a day before and on the day of coronary catheterization, is more beneficial in preventing CIN than ascorbic acid, particularly in diabetic patients with renal insufficiency undergoing coronary angiography.

Sadat et al **[167]** have carried out a meta-analysis with 1536 patients who completed the trial:

patients receiving ascorbic acid had a 33% less risk of developing CIN.

The antioxidant vitamin E has been also used to prevent CIN. Tasanarong et al **[168]** have found that the oral administration of either 350 mg/day of α-tocopherol or 300 mg/day of γ-tocopherol (5 days prior to the coronary procedure and continued for a further 2 days post-procedure) in combination with 0.9% saline (1 mL/kg/hour for 12 hours before and 12 hours after) is effective in protecting against CIN in patients with CRF undergoing coronary procedures with Iopromide (LOCM): CIN developed in 14.9% of cases in the placebo group, but only in 4.9% and 5.9% in the α- and γ-tocopherol groups, respectively.

Nebivolol is a third-generation β_1-adrenergic receptor antagonist **[169, 170]**. It has been used to protect the kidney against CIN through its antioxidant and NO-mediated vasodilating action. Toprak et al **[171]** have performed an experimental study in rats and have found that nebivolol decreases medullary congestion, protein casts and tubular necrosis, systemic and renal oxidative stress, proteinuria secondary to IRCA, and that it increases the kidney nitrite level decreased by IRCA. Nebivolol has been used at a dosage of 5 mg/day for one week or 5 mg every 24 hours for 4 days demonstrating a decrease of the incidence of CIN in patients with renal dysfunction undergoing coronary angiography **[172, 173]**.

A protective effect of the active vitamin D analogue paricalcitol in the prevention of CIN has been demonstrated in an experimental model by Ari et al **[174]**. In this study, Wistar albino rats were divided into 4 groups: control group, paricalcitol group, CIN group and paricalcitol plus CIN group. Paricalcitol was given intraperitoneally at a dose of 0.4 mg/kg per day (once daily) for 5 consecutive days. CIN was induced at day 4 by intravenous injection of indometacin (10 mg/kg; intravenously), followed after 15 min by Nv-nitro-L-arginine methyl ester (L-NAME) 10 mg/kg and after further 15 min by 6 ml/kg high-osmolar radiological contrast agent meglumine amidotrizoate. The mean serum creatinine value was significantly lower ($p<0.034$) and the mean creatinine clearance value was significantly higher ($p<0.042$) in the "Paricalcitol plus CIN group" than in the "CIN group". Mean serum malondialdehyde (MDA) **[175]** levels, which are end products, together with kidney thiobarbituric acid-reacting substances (TBARSs), of lipid peroxidation of membrane polyunsaturated fatty acids by free radicals and thereby indicators of oxidative damage, were also significantly lower in the "Paricalcitol plus CIN" group than in the CIN group ($p<0.024$). Similarly, mean TBARSs levels were significantly lower in the "Paricalcitol plus CIN group" than in the "CIN Group" ($p<0.042$). The increase in renal tissue and serum MDA levels and renal tissue TBARS levels by IRCA has been observed in experimental CIN models **[171, 176, 177]**. In addition, paricalcitol had been shown to improve cardiac oxidative

injury in uremic rats, and aortic oxidative injury in atherosclerotic rats **[178, 179]** and also to attenuate cyclosporin A induced nephropathy by suppression of inflammatory and apoptotic factors through inhibition of some protein kinase-signalling pathways **[180]**. Interestingly, Ari et al also showed that mean scores of tubular necrosis ($p<0.024$), proteinaceous casts ($p<0.038$), renal medullary congestion ($p<0.035$) and VEGF immunoexpression ($p<0.018$) in the "paricalcitol plus CIN group" were significantly lower than the ones obtained in the "CIN group". Thus, in their report the Authors conclude that paricalcitol causes a reduction in the unfavourable histopathological findings of CIN, possibly through its antioxidant effects by inhibition of lipid peroxidation and that, although further experimental and clinical studies are necessary, their findings provide evidence that paricalcitol has a significant potential as a therapeutic intervention for the prevention of CIN.

Many studies have demonstrated a beneficial effect of statins to prevent CIN in patients undergoing percutaneous coronary intervention **[181-186]**. On the other hand, hypercholesterolemia has been suggested as a predisposing factor to CIN. We have mentioned the study of Yang et al **[120]** demonstrating that long-term hypercholesterolemia in the rats is a risk factor for CIN. The nephroprotective effect of statins has been attributed to their antioxidant, anti-inflammatory, and antithrombotic properties and to their vasodilator property mediated by NO, that improves renal microcirculation **[187, 188]**.

Han et al **[189]** have demonstrated that rosuvastatin, at a dosage of 10 mg/day for five days, two days before, three days post the procedure, reduced the risk of CIN in patients with diabetes mellitus and chronic kidney disease undergoing coronary/peripheral arterial angiography. Al-Otaibi et al **[187]** have observed that simvastatin had a dose-dependent nephroprotective effect in experimental rats treated with IRCA. Patients on pravastatin had a lower incidence of CIN than patients on simvastatin **[190, 191]**.

Acikel et al **[192]** have demonstrated that short-term atorvastatin (40 mg/day 3 days before the procedure) as well as chronic atorvastatin therapy had a protective effect on renal function after coronary angiography. In the study of Patti et al **[193]** patients undergoing percutaneous coronary intervention were given short-term pretreatment with atorvastatin (80 mg 12 hours before intervention with another 40-mg pre-procedure, followed by long-term treatment of 40 mg/ day); this prevented CIN and shortened hospital stay.

As we have mentioned in the Pathogenesis section above, outer medulla hypoxia is due (a) to low O_2 delivery for anatomical reasons and (b) to the high O_2 consumption due to the high active sodium reabsorption in the thick ascending limb of Henle' loop. Since IRCA cause increased delivery of tubular fluid to the thick ascending limb of Henle's loop, thereby increasing the

active sodium reabsorption, it has been thought that furosemide, by decreasing sodium reabsorption in this tubular segment, would reduce medullary hypoxia, that is a crucial factor in the IRCA nephrotoxicity. But several studies have demonstrated no protection against CIN of this diuretic or even deleterious effects **[194-196]**. Thus, diuretics should be avoided before contrast exposure **[109]**.

We have to mention, however, the Renal Guard system™ for the combined use of furosemide and hydration to prevent CIN **[197, 198]**. In brief, as described by Briguori C. et al **[198]**, this RenalGuard system™ would guide the physician in achieving high urine output with furosemide while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia. The device includes a closed-loop fluid management system, a high-volume fluid pump, a high accuracy dual weight measuring system, motion-detection artifact reduction, a single-use intravenous set and urine collection system that interfaces with a standard Foley catheter, real-time display of urine and replacement fluid volume, timely alerts to drain the urine bag or to replace the hydration fluid bag, and safety features such as automatic air and occlusion detection. However, additional studies are still necessary to define the role of RenalGuard therapy in preventing CIN, taking also into account both safety and cost-effectiveness.

We have mentioned that after IRCA injection, NCX may reversely extrude Na^+ for Ca^{2+} influx and result in intracellular Ca^{2+} overload, that is believed to be a key factor in ischemic cell injury in CIN **[102]**. Thus, calcium channel blockers have been hypothesized to have protective effects against CIN. But their use have given controversial results, protective for some Authors **[199, 200]**, non protective according to others **[89, 201]**.

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Abbreviations: IRCA: Iodinated radiographic contrast agents; **SCr**: serum creatinine; **RBF**: renal blood flow; **CRF**: chronic renal failure; **ACEi**: angiotensin-converting enzyme inhibitors; **ARBs**: angiotensin II receptor blockers; **CIN:** Contrast-Induced Nephropathy; **CI-AKI**: Contrast-Induced Acute Kidney Injury; **CT:** computed tomography; **MDRD:** Modification of Diet in Renal

Disease; **eGFR:** estimated glomerular filtration rate; **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration; **LOCM:** Low-Osmolar Contrast Media; **NO:** nitric oxide; **ROS:** reactive oxygen species; **HOCM:** High-Osmolar Contrast Media; **IOCM:** Iso-Osmolar Contrast Media.

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