

Contrast Nephropathy: A Paradigm for Cardiorenal Interactions in Clinical Practice

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1. Introduction

Contrast-induced nephropathy (CIN) is defined as acute deterioration of renal function after intravascular administration of iodinated contrast agents, in the absence of other causes. Laboratory diagnosis is expressed as an increase in serum creatinine levels of 0.5 mg/dL (or 44 $\mu\text{mol/L}$) or a 25% or greater relative increase from baseline 48-72 hours after a diagnostic or interventional procedure, even if the clinical significance of this definition in the absence of pre-existing renal failure is questionable (Thomsen & Morcos, 2006).

The Acute Kidney Injury (AKI) Network was established in 2007 to study the improvement of outcomes associated with various forms of acute renal failure; recently, it has expressed the hope that the diagnostic criteria for all cases of acute kidney injury are standardized in sudden reduction (within 48 hours) of renal function with a serum creatinine increase ≥ 0.3 mg/dL or a 50% or greater increase from baseline, or after onset of oligoanuria (urinary output < 0.5 mL/kg/hour for 6 hours) (Mehta et al., 2007).

However, there is no consensus in bringing CIN parameters in AKI criteria, because contrast medium damage usually causes a serum creatinine peak on the third-fifth day after contrast medium exposure, and rarely occurs with oligoanuria, except in patients with advanced impairment of renal function (Detrenis et al., 2007a). Nevertheless, recent literature uses the term "radiocontrast-induced acute kidney injury" (RCI-AKI) rather than CIN, although the clinical implications of different definitions have never been tested on a large scale (Goldfarb et al., 2009).

2. Epidemiology

RCI-AKI is today the third nosographic entity related to hospital-acquired acute renal failure, after organ hypoperfusion and nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) (Nash et al, 2002). RCI-AKI incidence is significantly greater in the case of intra-arterial (from 10-20% for moderate to 25-70% for high-risk patients; 0.15-2.30% in general population) compared to intravenous administration (~5%) (Detrenis et al., 2007a).

The probability of renal replacement therapy is closely related to individual patient comorbidities, but it is reasonable to assume that it varies from less than 1% of all patients undergoing percutaneous coronary intervention to 10% of those with pre-existing alteration in renal function parameters who have RCI-AKI after coronary angiography (Meschi et al., 2006). In other words, the probability of RCI-AKI requiring dialysis increases from 0.04 to 48% if measured glomerular filtration rate is reduced from 50 to 10 mL/min; on the other hand, 13-50% of subjects undergoing dialysis after RCI-AKI tends to prolong renal replacement therapy definitively (Toprak, 2007).

As in general for nephropatic patients, even for those affected by RCI-AKI the incidence of associated cardiovascular events or major adverse cardiac effects was assessed: a study on 16.000 hospitalized subjects who underwent coronary angiography (Levy et al., 1996) shows that those with RCI-AKI develop a risk for complications and death 5-fold higher than in controls, even after data correction for any existing comorbidities. Even for the majority of cases, with benign clinical course (pre-existing serum creatinine values restoration in 1-3 weeks, no symptoms or dialysis), there was a significant increase in 1- and 5-years mortality (Rihal et al., 2002). This evidence is greater for cases with unfavourable renal prognosis requiring temporary renal replacement therapy (McCullough et al., 1997).

Consequently, even if the pathophysiological relationship between contrast nephropathy, morbidity and mortality it is not clear, RCI-AKI is today definitely considered an independent predictor for long term mortality. It is possible to hypothesize that the pathogenic process underlying RCI-AKI may interfere with pro-atherogenic mechanisms of cardiovascular disease, although there are no definitive studies on this issue (Detrenis et al., 2005).

3. Risk markers for contrast nephropathy

The pathogenetic events underlying RCI-AKI are still not completely understood and the identification of “risk factors” for disease is difficult, because the term usually refers to a medical condition or nosographic entity associated with a therapeutic intervention or preventive approach. It is therefore considered that the term “marker” is more useful to identify patients predisposed to acute deterioration of renal function in this context, due to specific pathophysiological features (Toprak, 2007).

In one third of cases, these markers do not correspond to changeable conditions. Instead, the early recognition of remaining situations becomes a prerequisite to the use of prophylactic protocols. Even in the absence of incontrovertible evidence, these protocols have shown a variable reduction in the incidence of RCI-AKI during prospective or retrospective studies (Toprak, 2007) (**Fig. 1**).

3.1 Advancing age, chronic nephropathy and accurate assessment of renal function

Between markers of risk, the reduction in renal function before the administration of iodinated contrast medium plays a predominant significance, particularly if baseline glomerular filtration rate values are $< 60 \text{ mL/min/1.73 m}^2$, that is in the course of chronic kidney disease at stage 3, 4, 5 for the National Kidney Foundation (Nelson & Tuttle, 2007).

The decrease of renal function can not be revealed by routine measurement of serum creatinine, because there is an inverse, non-linear relationship between serum creatinine (varying with the muscle mass, age and sex of the patient) and corresponding glomerular filtration rate. In any case, glomerular filtration rate tends to decrease progressively with increasing age and can be measured indirectly by creatinine clearance (Detrenis et al., 2007b). A recent analysis of more than 20000 patients undergoing coronary angiography showed that there is a significantly higher incidence of RCI-AKI in the elderly, especially women, who usually have a net reduction of glomerular filtration rate even when there is an apparently normal serum creatinine. Indeed, a relative reduction in muscle mass is frequently observed in these subjects (Sidhu et al., 2008) (Fig. 2).

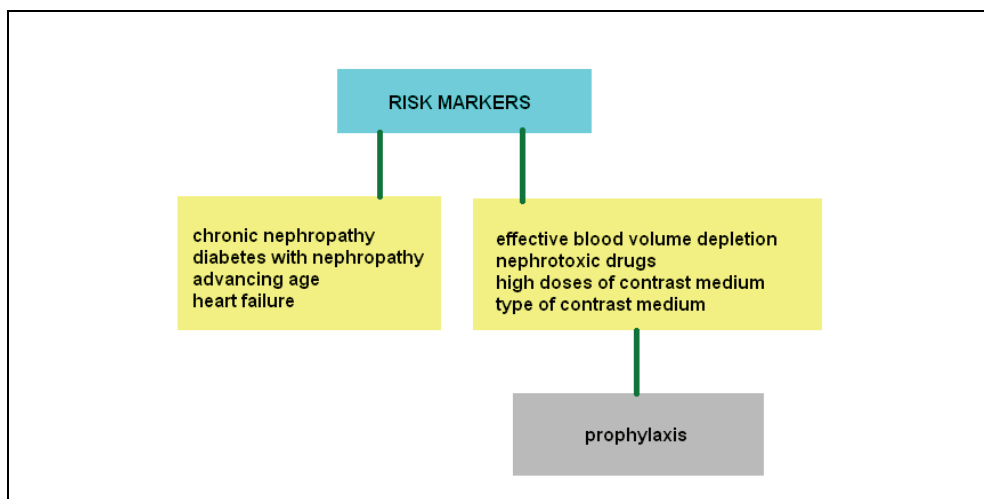


Fig. 1. Risk markers for contrast nephropathy

When the creatinine clearance (1) is not easily achieved through the urinary output collection, so-called MDRD or Levey equation (from the Modification of Diet in Renal Disease Study) (2) can be used to estimate glomerular filtration rate (Levey et al., 1999). However, the simple evaluation of creatinine clearance by classical Cockcroft and Gault formula (3), which consider daily urinary creatinine and only requires knowledge of body weight, age and sex of the patient, it is appropriate to clinical practice (Cockcroft & Gault, 1976).

$$\text{creatinine clearance} = \frac{\text{urine creatinine} \times \text{daily urinary output}}{\text{serum creatinine} \times 1440} \tag{1}$$

$$\text{creatinine clearance} = \frac{(140 - \text{age}) \times \text{body weight}}{\text{serum creatinine} \times 72} \times 0.85 \text{ (if female)} \tag{2}$$

$$\begin{aligned} \text{estimated GFR} &= 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female)} \\ &= 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 1.210 \text{ (if afro-american)} \\ &\text{(for 1.76 m}^2 \text{ body surface area)} \end{aligned} \tag{3}$$

Cystatin C, produced at a constant rate by nucleated cells and released into circulation (normal values <0.95 mg/L in subjects aged < 45 years, up to 1.2 mg/L in older), was recently identified as a marker of renal injury early and easily measurable. It is freely filtered by the glomerulus and completely reabsorbed and metabolized, but not secreted by cells of the proximal tubule. Furthermore, it is not subject to significant urinary excretion, and is not affected by gender or muscle mass of the patient (Perkins et al., 2005).

Some studies have used direct measurements of glomerular filtration rate as a gold standard to compare the use of cystatin C with serum creatinine and serum creatinine-based assessments, demonstrating the superiority of the former especially in diabetic patients (Perkins et al., 2005).

The data on clinical use of this method, however, are controversial. The serum concentrations of cystatin C identify a condition of preclinical renal damage earlier than other laboratory parameters, and are also a possible risk marker for heart failure and other cardiovascular events in elderly patients. On the contrary, is not yet clear the real influence of other factors (cigarette smoking, thyroid disease, high levels of C-reactive protein, corticosteroid therapy) on these measurements (Burkhardt et al., 2002).

In other words, the accuracy of this diagnostic test has been documented when the sensitivity of serum creatinine measurement is reduced. However, cystatin C can be interpreted not only as a marker of renal function, but also as generic indicator of inflammatory processes (Burkhardt et al., 2002). In addition, quantitative data on extrarenal clearance of the molecule are not available. Therefore, because its early serum increase (within 24 hours after contrast administration) it could be a useful parameter for RCI-AKI after angiographic procedures, but requires further prospective evaluation for large-scale use (Detrenis et al., 2007b).

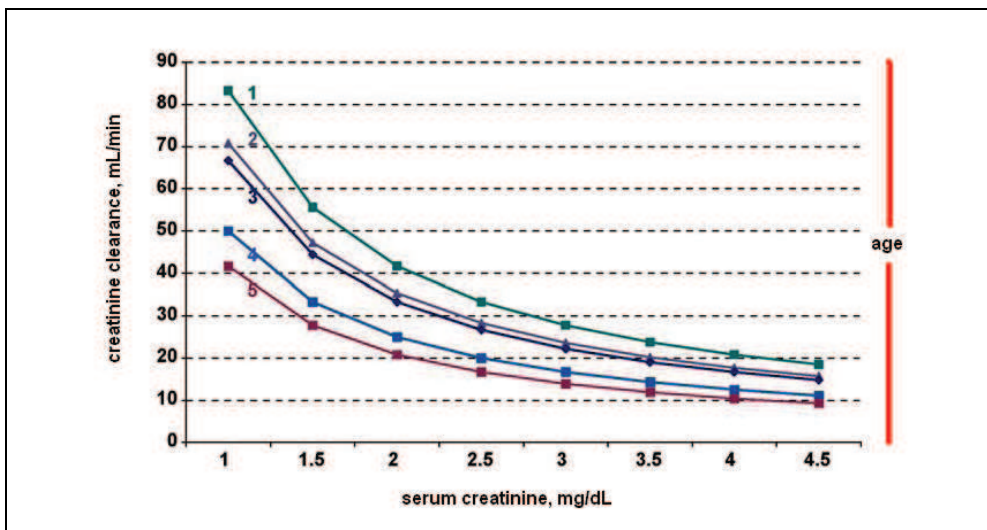


Fig. 2. Serum creatinine, creatinine clearance and age. 1: male, 60 kg, 40 years. 2: female, 60 kg, 40 years. 3: male, 60 kg, 60 years. 4: male, 60 kg, 80 years. 5: male, 60 kg, 90 years

3.2 Impaired fasting glucose, diabetes mellitus and its complications

Between changes in carbohydrate, lipid and protein profile (dyslipidemia, hyperuricemia, metabolic syndrome), diabetes mellitus – according to definition in use, two measurements of fasting plasma glucose > 126 mg/dL – does not seem constitute an additional risk for RCI-AKI in itself, but only if there is consequent impairment of renal function (Parfrey PS et al., 1989).

Conversely, a prospective evaluation suggests a slight, but significant increase in the incidence of RCI-AKI in diabetic, non-nephropatic subjects, and even for those with impaired fasting glucose, compared to the general population (Toprak et al., 2007).

This is consistent with the hypothesis that the so-called endothelial dysfunction contributes to development of disease. In fact, it is present in all the above conditions of dysglycemia. At the level of the renal glomerulus, it leads to reduced availability of vasodilatory substances, such as nitric oxide and prostaglandins, which are synthesized in the endothelium. In this way, the renal ischemia associated with administration of iodinated contrast is encouraged, through the role of oxygen free radicals, which are able to induce the formation of reactive species in enzymes and membrane protein structures, using mechanisms of nitrosylation and oxidation (Detrenis et al., 2005).

3.3 Dehydration and relative hypovolemia

Even patients with heart failure and low cardiac output leading to reduced renal perfusion should be considered at increased risk for RCI-AKI (Thomsen & Morcos, 2003). This condition may worsen hypoxia and ischemia of the kidney caused by iodinated contrast agents. After an initial vasodilation, contrast media lead to a prolonged vasoconstriction in the medulla of the nephron, which already is less perfused than the cortex (Detrenis et al., 2005).

Subjects with the effective blood volume depletion, peripheral hypoperfusion, hypotension can be found under the same conditions. A similar trend is observed during sepsis, liver disease with severe hypoalbuminemia and dysproteinaemia, or in severe protein loss from any cause (Savazzi et al., 1997).

Periprocedural hydration and consequent volume expansion of the patient appear as the only safe options for RCI-AKI prophylaxis. They stimulate physiological diuresis and dilute concentrations of contrast medium and circulating mediators of vasoconstriction (adenosine, endothelin, angiotensin II). Therefore, true effectiveness of parenteral infusion protocols does not depend on the characteristics of the fluids used, or peculiar infusion rate. The use of solutions of sodium bicarbonate (154 mEq/L, 3 mL/kg/hour to 1 hour before the procedure, 1 mL/kg/ hour in the next 6 hours) (Merten et al., 2004) or isotonic saline (1 mL/kg/hour, 12 hours before and 12 hours after the procedure) (Mueller et al., 2002) is designed to correct the evident or latent depletion of the extra- and intracellular body compartments (Meschi et al., 2006).

4. Iodinated contrast media and other drugs

High-osmolal appear to be more nephrotoxic than current low-osmolal contrast media and recent iso-osmolal dimers, which did not demonstrate a favorable cost-effectiveness ratio (Savazzi et al., 2005; Detrenis et al., 2007c).

Although the CM-induced renal damage is dose-dependent, the volume below which the risk is reduced has not been identified, particularly when there is a preexisting decrease in renal function associated with diabetes (Meschi et al., 2006).

The intra-arterial route of administration (eg, interventional cardiology) is associated with an increased risk of RCI-AKI that the intravenous (eg, computed tomography), especially when examinations are repeated in succession at an interval of time less than 72 hours (Detrenis et al., 2007a).

In the case of concomitant use of contrast media, it is mandatory to avoid traditional nephrotoxic drugs (eg aminoglycosides), as well as nonsteroidal anti-inflammatory drugs, which can reduce the filtrate due to inhibition of intrarenal vasodilatation (Meschi et al., 2006).

The continuous treatment with agents that interfere with the renin-angiotensin system (angiotensin converting enzyme inhibitors, angiotensin receptor antagonists) contribute to the increase in the incidence of RCI-AKI in patients with chronic kidney disease. In fact, they cause efferent arteriolar vasodilation and thus the relative reduction of pressure within the glomerulus. According to some evidence, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics should be discontinued the day before and day of the procedure with contrast, and should be taken after 2 days, unless contraindicated (Komenda et al., 2007; Cirit et al., 2006). However, more recent studies refute the efficacy of withdrawal (Rosenstock et al., 2008); on the contrary, telmisartan may play a protective role, at least in animals (Duan et al., 2009).

Extreme caution must be observed in the administration of contrast media in patients with diabetes treated with metformin. In fact, renal failure caused or worsened by concomitant AKI-RCI tends to result in a significant accumulation of biguanide, with possible development of lactic acidosis (Thomsen & Morcos, 1999).

5. The myth of monoclonal gammopathies

Until a few years ago, many clinicians prescribing the so called "screening for Bence Jones proteinuria" before performing an examination with contrast medium (Strada et al., 2008). Many laboratories provided (and still provide) a report in mg/dL, compared with a normal range (0 - 0.8 mg/dL). With this system, "Bence Jones proteinuria" greater than 0.8 mg/dL was defined as positive.

Many criticisms can be conducted in this model. Under normal conditions, immunoglobulin light chains (kappa, lambda) are freely filtered by the glomerulus and subsequently reabsorbed from the tubule to 99%. A normal urinary excretion of light chains is estimated at 20-40 mg per day (Strada et al., 2008). This amount increases significantly in case of impaired tubular reabsorption, for example during tubule-interstitial nephropathy, but concerns polyclonal light chains that are not of neoplastic origin.

On the contrary, the real Bence Jones protein was first described in 1962 as "consisting of monoclonal light chains" and produced by a single clone of B lymphocytes. It appears in the urine when the efficiency of tubular reabsorption is saturated, as in the course of diseases such as multiple myeloma, Waldenstrom's macroglobulinemia and lymphoproliferative

disorders (Strada et al., 2008). For this reason, a pathological parameter (M monoclonal component), which under normal conditions should not be detected, can not be expressed in a range defined as physiological (0 – 0.8 mg/dL).

Moreover, despite the monoclonal gammopathies have been reported as risk markers for RCI-AKI for a long time, all the reviews of the scientific literature indicate that the association between the two comorbidities occurs only if a severe depletion of water and blood volume of the patient is demonstrated, or when the hematological malignancy has led to renal failure or hypercalcemic syndrome.

Thus, the monoclonal gammopathies should not be considered as primary contributing factors of the RCI-AKI, and screening of the so-called Bence Jones proteinuria has no clinical significance in patients undergoing contrast media (Meschi et al., 2006; Toprak, 2007). The presence of monoclonal gammopathy should be considered critically and the procedure with contrast medium, when necessary, can be implemented after evaluating volume, fluid and electrolyte status and renal function of the patient (Fig. 3).

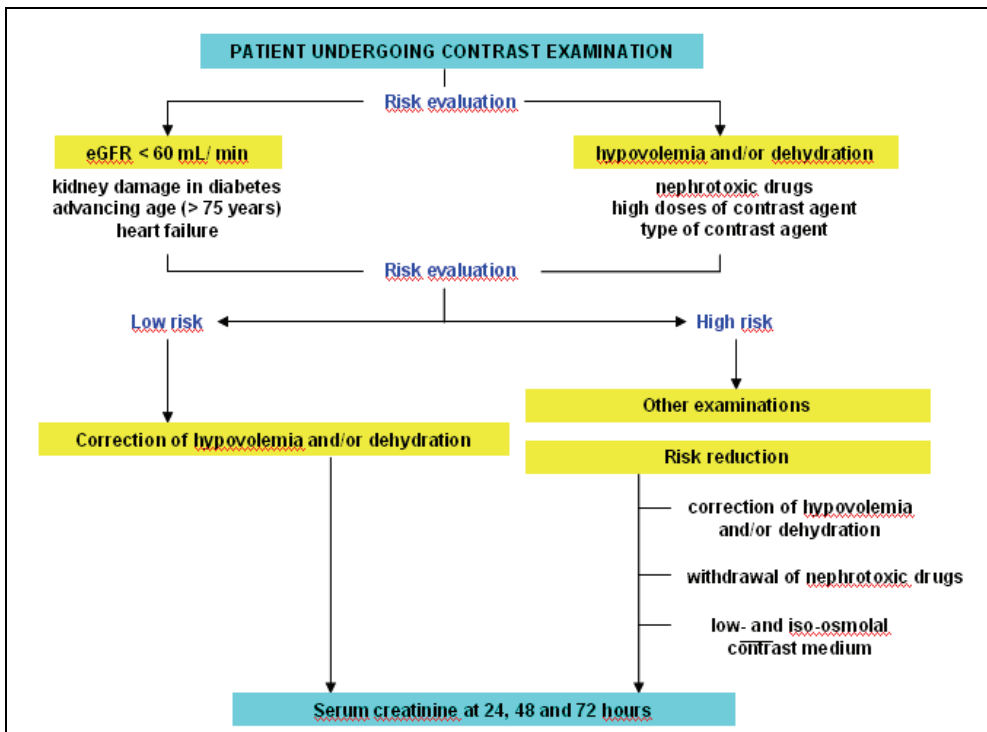


Fig. 3. Management of the patient undergoing contrast medium examination.

6. Acknowledgment

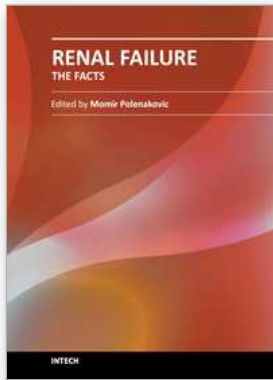
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Renal Failure - The Facts

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The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenesis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is great medical problems and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological condition in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter a nephrological problems in their day-to-day practice.

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