

New Aspects of Contrast Nephropathy in Cardiology

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Advances in imaging techniques for diagnostic purposes and for guiding percutaneous coronary interventions and the demographic changes in the population mean that increasing numbers of patients are undergoing studies with iodine contrast agents.

When no recognized risk factors are present and renal function is normal, exposure to such agents does not require any special caution. However, elderly patients and patients with diabetes, hypertension, heart disease, and kidney disease, that is, those who stand to benefit most from the aforementioned interventional techniques, are also those at greatest risk of contrast nephropathy. Magnetic resonance imaging techniques, initially considered the best diagnostic alternative in patients at high risk of contrast nephropathy, are not a substitute for invasive techniques when endovascular treatment is needed. Furthermore, the use of gadolinium as a paramagnetic contrast for magnetic resonance imaging is contraindicated in patients with creatinine clearance below 30 mL/min due to the risk of developing nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD), as recently recognized by the Food and Drug Administration.¹

The 2 fundamental criteria proposed by the Spanish Society of Nephrology to define the appearance of contrast nephropathy are an absolute increase in plasma creatinine of 0.5 mg/dL with respect to baseline or a relative increase of 25% of iodine contrast 24-48 hours after administration,² in absence of other documented causes for renal failure (atheroemboli, aortic dissection, etc). Table 1 shows the recommendations for recognizing the onset of contrast nephropathy.

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TABLE 1. Evaluation of Contrast Nephropathy¹

Assess risk/benefit of the study
Measure creatinine, estimate baseline CCI
Measure creatinine at 24 hours and 48 hours
Monitor diuresis
Contrast nephropathy occurs if:
1. Creatinine increases by 0.5% or
2. Creatinine increases by 25% with respect to baseline
Monitor creatinine until it returns to baseline value
Avoid further contrast use and nephrotoxic substances

However, the use of other criteria for acute renal failure in different series makes comparison between series more difficult.³ At times, renal failure is defined as serum creatinine >2 mg/dL,⁴⁻⁷ >3.4 mg/dL,⁸⁻¹⁰ and even >6 mg/dL.¹¹ On other occasions, the criterion used is an absolute increase in creatinine of 0.5 mg/dL¹² or 1 mg/dL¹³ with respect to baseline. A relative increase of serum creatinine of 50%⁵ or 100%^{4,8} compared to baseline has also been used. Although a single consensus has not yet been reached, the current tendency is toward defining acute renal failure according to the decrease in glomerular filtration calculated with algorithms based on serum creatinine.¹⁴

This issue of the journal contains 2 original articles which investigate crucial aspects of the increasingly common problem of contrast nephropathy.

In the article by Bouzas Mosquera et al,¹⁵ the cardiology group at the Hospital Juan Canalejo, in La Coruña, Spain, present their 4-year experience in a very special group of patients: those who, because they have ST-elevation acute coronary syndrome and require emergency catheterization, have a very limited time window for preventative maneuvers. The 602 patients analyzed in the study meet these criteria. Some of the characteristics of the study design mean that the data cannot be generalized to other situations of contrast nephropathy: the contrast used (iohexol) is considered to be low osmolar but is hyperosmolar with respect to plasma, and all patients received acetylsalicylic acid and abciximab before the procedure. Furthermore, all patients had acute coronary syndrome. Such patients are at greater

risk of contrast nephropathy. In a review of 7500 patients of similar characteristics to those described by the aforementioned Galician group, the incidence of contrast nephropathy was 25% in those whose baseline plasma creatinine levels were ≥ 2 mg/dL.¹⁶ In the study by Bouzas Mosquera et al,¹⁵ the overall incidence of contrast nephropathy was 12%.

In most cases, acute renal failure associated with contrast nephropathy is reversible. Current opinion is therefore posing the question of whether the appearance of an event such as contrast nephropathy is really serious or relevant given that it will probably be self-limiting. Long-term studies on the outcomes of patients who presented with acute renal failure of any cause during their stay in hospital are few and heterogenous, and so the influence of this condition on medium- and long-term cardiovascular prognosis is almost completely unknown.

In 1 study, recently published by the group led by Liaño et al¹⁷ of the Hospital Universitario Ramón y Cajal in Madrid, Spain, 187 patients who survived a total of 413 cases of acute renal failure were sequentially studied between 1977 and 1992. The patients were reassessed after at least 7 years had passed. Of these patients, 56% had died in the intervening period, and in 59% the cause of death was related to acute renal failure. Survival at 1, 5, 10, and 15 years after renal failure were 89%, 67%, 50%, and 40%, respectively. Among the surviving patients, renal function was normal in 81%.¹⁷

The study by Bouzas-Mosquera et al¹⁵ offers particularly useful information on the influence of renal failure on long-term cardiovascular prognosis: renal failure related to use of contrast was a strong predictor of all-cause mortality, cardiovascular mortality, major cardiovascular events, and need for revascularization procedures. However, as reported by Liaño et al,¹⁷ the long-term impact on renal function, in terms of need for dialysis, was minimal.

It might be interpreted that renal failure acts as a biomarker of the severity of the underlying cardiovascular disease: the more severe the heart disease, the more severe the renal involvement (lower load, greater use of angiotensin converting enzyme inhibitors or angiotensin II antagonists, more intensive diuretic treatment, greater extracardiac vascular disease, etc). But this interpretation is probably too simplistic. It could be that there are other relationships between the appearance of renal failure and poor cardiovascular prognosis. For several years now, renal failure has been recognized as an independent cardiovascular risk factor,^{18,19} probably due to its proinflammatory nature. Oxidative, nitrosylative and inflammation mediators have been proposed as possible mechanisms for this harmful effect.^{20,21} It could be that activation of the renin-angiotensin system plays its own role.²² But in addition, the appearance of acute renal failure can block the synthesis of erythropoietin,^{23,24} whose endothelial

TABLE 2. Model for Predicting Contrast Nephropathy^{26,a}

Variable	Points
Hypotension (SBP < 80 mm Hg for at least 1 h ^b)	5
IABC	5
CHF	4
Age > 75 y	4
Baseline renal function	
Creatinine > 1.5 mg/dL or	4
GFR < 20 mL/min 1.73 m ²	6
GFR < 20-40 mL/min 1.73 m ²	4
GFR < 40-60 mL/min 1.73 m ²	2
Anemia (hematocrit < 39% in men and < 36% in women)	3
DM	3
Contrast volume	1 for every 100 mL of contrast

^aDM indicates diabetes mellitus; GFR, glomerular filtration rate estimated with the simplified MDRD equation; IABC, intra-aortic balloon counterpulsation; SBP, systolic blood pressure; CHF, chronic heart failure.

^bRequiring inotropic support or IABC within 24 hours of the procedure.

protective effect²⁵ and regulation of endovascular cell migration and angiogenesis are beginning to be recognized.²⁶ Knockout mice lacking the erythropoietin gene did not get to show changes in fetal erythropoiesis given that the embryos died much earlier due to lack of development of the heart.²⁶

The authors make an exhaustive analysis of the risk associated with different demographic, clinical, and hemodynamic variables. Of particular interest is the analysis of the influence of the type, site, and treatment of myocardial infarction in the development of contrast nephropathy. In the conclusions, the authors present a risk classification different to the traditionally accepted one of Merham²⁷ (Table 2), but, without doubt, the one used by the authors is more appropriate for the subgroup of patients included in their study.

Finally, a notable fact widely observed but not often published and certainly not analyzed is that inhibition of the renin-angiotensin system during procedure itself increases the risk of contrast nephropathy.¹⁵

If the first of these studies published in this issue of the *Revista Española de Cardiología* concerns the risk factors in cardiovascular prognosis associated with contrast nephropathy, the second study concerns several aspects relevant to risk prevention.²⁸

Antioxidants, vasodilators, plasma expanders, diuretics, and preventive hemodialysis have been proposed as useful methods for preventing contrast nephropathy^{2,29}; Table 3 shows the current level of evidence to support these approaches.²

TABLE 3. Evidence-Based Recommendations for Prevention of Contrast Nephropathy^{1,a}

Renal failure (CCI <60) is a risk factor for contrast nephropathy	Level A
The high osmolality of IC have a higher risk than low ones	Level A
Prior hydration with intravenous fluids is effective	Level A
Hydration with isotonic saline is superior to hypotonic saline	Level A
Hydration with bicarbonate (154 mEq/L) is superior to saline	Level B
Oral hydration in the 24 hours prior to the procedure is inferior to intravenous hydration but is useful and should be done	Level C
Prophylaxis with diuretics, mannitol, ANP, dopamine, antiendothelin antibodies, fenoldopam, contraindicated in contrast nephropathy	Level A
Prior prophylaxis with NAC and on the day of IC may be useful	Level B
Hemofiltration before and after the procedure can be considered in high-risk patients admitted to the ICU	Level B

^aIC indicates iodated contrast; NAC, N-acetylcysteine; ANP, atrial natriuretic peptide; ICU, intensive care unit.

Of these preventative approaches, without doubt the most widely accepted ensuring the subject is well hydrated prior to contrast infusion. Nevertheless, many questions are still awaiting resolution: How do fluids exert their protective effect?

– Through intrahepatic and atrial expansion, with the corresponding stimulation of natriuretic factors that increase filtration and reduce sodium retention?

– Through expansion of arterial volume, thereby inhibiting the sympathetic tone and canceling the activation of the renin-angiotensin II system?

– Through expansion of the intracellular volume thereby protecting tubule cells against a hyperosmotic aggression and inhibiting secretion of vasopressin to allow a larger diuresis volume in a shorter time?

– Through a change in the ionic characteristics of urine thereby modifying the solubility of the contrast?

– Through inhibition of proximal sodium transport, thereby reducing toxic accumulation of contrast in the given segment and modulating local synthesis of NO and free radicals?

If we knew the detailed mechanism of the appearance of contrast nephropathy, we could answer these questions and choose the best hydration regimen:

– Is prolonged hydration or bolus expansion preferable?

– Is expansion with saline solution or bicarbonate solution the best option?

– Is expansion with isotonic or hypotonic saline solution the best option?

In this issue of the journal, Marrón et al²⁸ of the Fundación Jiménez Díaz publish a study entitled “Systemic and Renal Effects of Preventing Contrast Nephrotoxicity With Isotonic (0.9%) and Hypotonic (0.45%) Saline.” The study did not aim to determine which of the 2 protocols is most beneficial for preventing

contrast nephrotoxicity, but rather to determine what hemodynamic and renal repercussions might be expected when using either of the 2 hydration protocols currently most used in clinical practice for preventing contrast nephropathy.

When the criteria of Mehran¹⁷ are applied to patients of this study, the risk of contrast nephropathy according to the clinical and demographic data presented is 10%; if the score of Bouzas-Mosquera et al¹⁵ is applied, the risk is 9%. The incidence observed by the authors was 13% and 12% in the 2 arms of the study. Although the example is anecdotal, it is possible to see up to what point the use of predictive tables of renal failure begins to be reliable in contrast nephropathy.

Some of the data presented by Marrón et al²⁸ are extremely interesting. For example, with the hydration volumes used in one or the other group, the volume expansion never managed to cause a significant increase in the secretion of atrial natriuretic peptide. However, there was a clear inhibition of sodium retention, whose fractional and absolute excretion increased in the first 24 hours before subsequently decreasing. This natriuresis appears to be independent of the type of solution. Likewise, diuresis increases with both types of saline in the first 24 hours. Interestingly, in the group that underwent hypotonic infusion, osmolar clearance did not vary despite infusion of contrast, and so the diuretic and natriuretic effect cannot be attributed to the contrast medium itself.

The sustained reduction in the transtubular potassium concentration gradient, although small, indicates that both saline infusion protocols cause a decrease in the effect of aldosterone on the distal nephron, and once again points to a possible role of the renin-angiotensin-aldosterone system in intrarenal hemodynamics after administration of iodine contrasts.

Finally, greater intake of free water and lower sodium intake in the hypotonic infusion leads, as expected, to a lower plasma expansion (hardly 3%) and greater cellular

hydration, judging from the smaller renal effect of vasopressin observed.

Although the study was not designed to analyze differences in protection against contrast nephropathy between the 2 therapeutic regimens (due to the low number of events, the power of comparison for incidence of contrast nephropathy is 4% after 24 hours and 16% after 48 hours), there was a certain favorable tendency toward use of hypotonic saline. Although the evidence in favor of isotonic saline is considered level A (Table 3), this evidence is based mainly on the study of Mueller³⁰ in 1620 patients undergoing coronary artery angioplasty and randomly assigned to 2 treatments practically identical to those used in the study of Marrón et al.¹⁵ But unlike the study of Marrón et al,¹⁵ 60% of the patients in the study of Mueller et al³⁰ had emergency coronary angiograms and could benefit from the hemodynamic effects of acute infusion of isotonic saline.

It may be that both regimens are valid as prophylaxis against contrast nephropathy and that the choice should be tailored to the clinical state of the patient. In this case, the study of Marrón et al¹⁵ would help us to select which patients might benefit most in each case.

Taken together, the 2 studies published in this issue are a good example of problems arising from the technological development of medicine in Spain, reveal unexpected pathophysiological relationships, strengthen interdisciplinary ties, and allow more complete approaches to patient management although, in some cases, there are still many unknowns to clarify.³¹

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