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Contrast-induced nephropathy

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Acronyms
CIN: contrast-induced nephropathy
CRD: chronic kidney disease
GF: glomerular filtration rate
PCI: percutaneous coronary intervention

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ABSTRACT
Contrast-induced nephropathy is an important complication associated with the use of contrast media. Favoring factors for the development of contrast-induced nephronpathy have been widely described, being diabetes mellitus and previous renal disease the greatest risk. The pathophysiology is a complex process where the medullary hypoxia represents the trigger element. Previous hydration and the use of low osmolality contrast are the most recommended measures to prevent its development.
Key words: Kidney diseases, Contrast-induced nephropathy, Contrast media, Cell hypoxia, Disease prevention

Nefropatía inducida por contraste

RESUMEN
La nefropatía inducida por contraste representa un importante efecto adverso derivado de la administración de medios de contraste. Los factores favorecedores han sido ampliamente descritos entre los que destacan la diabetes mellitus y la enfermedad renal preexistente. La fisiopatología constituye un proceso complejo en el que la hipoxia medular constituye el elemento detonante. Las medidas preventivas mayormente recomendadas son la hidratación previa y el empleo de contraste de baja osmolalidad.
Palabras clave: Enfermedades renales, Nefropatía por contraste, Medios de contraste, Hipoxia de la célula, Prevención de Enfermedades

INTRODUCTION

In recent decades, an increasing use of imaging diagnostic techniques based on the use of iodinated radiologic contrast media has taken place, which are generally classified by their osmolality relative to the blood in: hyperosmolar, isosmolar and hiposmolar. Despite the clinical development of some contrasts took place over half a century ago, today there remains uncertainty about some of their key toxicities[1]. Although in most cases diagnostic and therapeutic procedures that require the use of contrast media are relatively safe, occasionally, complications may occur. One of

them has motivated a great interest in recent times: the contrast-induced nephropathy (CIN), which tends to appear immediately (24-72 hours) after the intravascular use of an iodinated contrast medium. The main aim of the following article is to conduct a systematic review of the topic.

DEFINITION AND EPIDEMIOLOGY

The currently accepted definition for the CIN is the elevation of serum creatinine basal figures at 0.5 mg/dl in the first 24-72 hours after exposure to a contrast medium[1]; also, other definitions have been formulated as increased basal levels of 1 mg/dl or a serum creatinine value above 25% relative to the basal value[2]. However, the criterion of CIN as an elevated creatinine greater than 0.5 mg/dl in the first 24-72 hours predicts higher rates of adverse cardiac events after six months of monitoring[3].

The incidence of CIN is variable according to the reference population and individual risk factors for each patient. An incidence of 0.6 to 2.3% has been reported, which can reach 6.1 to 8.5% in patients with chronic kidney disease (CKD)[4]. Other authors have communicated an incidence of 0-10%, even reaching up to 14.5% in interventional procedures[5], but in populations with previous diabetes mellitus and CKD the incidence may increase even up to 50%[6]. Also, in patients with comorbidities, high risk and hospitalized, it comes up to 38%, depending on the series of study[7].

RISK FACTORS

Risk factors that favor the development of CIN have been studied multiple times. They have been classified into 2 groups: 1) related strictly to the patient, where is included prior renal history affectation, advanced age, diabetes mellitus, use of nephrotoxic drugs, reduced left ventricular ejection fraction, low cardiac output, anemia, kidney transplants and hypoalbuminemia and 2) factors derived from the procedure, such as volume of the used contrast[8], use of contrasted agents of high osmolality, intra-arterial injection, multiple injections of contrast within less than 72 hours, and use of devices such as intra-aortic balloon pump[3].

The presence of CKD grade 3, defined as a renal glomerular filtration rate (GFR) <60 ml/min/1.73 m^2, is the more transcendent predisposing factor for the development of CIN after interventional procedures. Also, the presence of an elevated creatinine previous the procedure (≥3 mg/dl) increases the odds of acute renal failure's risk and higher hospital mortality. Moreover, it has been observed that the same risk is further increased with the association of elevated creatinine and diabetes[9], which has motivated the use of models for calculating CIN´s risk and it has taken into account predisposing risk factors. A predictive risk model widely known is the proposed by *Mehran et al.*[10], which includes risk factors such as: hypertension, use of counterpulsation balloon, heart failure, age over 75, diabetes mellitus, low hematocrit, average contrast volume, and GFR; therefore a scoring system is established, where a score below 5 infers a risk of 7.5% CIN and a need for dialysis of 0.04%, while a score above 16 represents a significant increase risk of CIN and dialysis[3]. Regarding the estimation for equations of the GFR, its obtaining is recommended from the measurement of serum creatinine, age, sex and ethnicity[11]. Using the Cockcroft-Gault equation, classically employed in adjusting drug dosage and which has also been referred to assess states of hyperfiltration, should be discouraged, because this equation was not restated to creatinine values obtained by proper procedures and it cannot be assumed for current creatinine measuring methods, whereas the equations of Chronic Kidney Disease Epidemiology Collaboration[12] and Modification of Diet in Renal Disease Study Group[13] can be used for this purpose, but the authors acknowledge that the first[12] is better because it is based on creatinine measurement standardized procedures. Although in general, the use of equations for estimating the GFR is inadequate in clinical situations such as: extreme body weight, special diets or malnutrition, impaired muscle mass, major amputations, liver diseases, pregnant women, acute renal failure and study of potential kidney donors.

In such cases, for an appropriate measure of renal function, urine collection of 24 hours is required to calculate the creatinine clearance[14]. Recently, the use of cystatin C or the estimated GFR has been proposed from it, as a screening parameter for CKD[15].

PATHOPHYSIOLOGY

Despite the clinical importance of the CIN, taking into account that it is the third leading cause of ia-

trogenic kidney disease in hospitalized patients, the pathophysiology remains entirely unclarified. Basically, the mechanisms involved include direct cytotoxic effect, autocrine and paracrine factors that affect renal hemodynamics, as well as alterations of the rheological properties of the tubular system and regional hypoxia. These factors may act synergistically in the pathophysiology *per se* and their action will depend on the contrast employed, on the pre-existing individual risk elements, and the hydration status of the patient prior to the procedure.

The renal medulla is an anatomical structure of vital importance and the effect of the hypoxia at this level is crucial in the CIN's pathophysiology. The outer portion of the medulla is particularly vulnerable to oxygen deficiency and this is due to the existing anatomical distance between the structure and the descending vasa recta (DVR), a structure covered of pericytes directly involved in the regulation of blood flow in charge of providing nutrients and primarily oxygen to the renal medulla[16], although this contribution takes place at a slow infusion rate, mediated by arteriovenous shunts at a microcapillary level. The contrast at this level produces an imbalance of interchange between the supply and consumption of oxygen by many mechanisms, mainly the blood hypoperfusion[17,18], which favors the increased resistance to mediated blood flow, among other factors, by vasoconstriction of the DVR, and this affects both the medullary and cortical levels. The cortical vasoconstriction or more precisely, the preglomerular, can reduce the flow in the medulla and the DVR; however, the fall in the GFR rate tends to reduce the demand for secondary oxygen to the reduction of reabsorption at the tubular level[19].

A peculiar element is the osmolality of the renal medulla, being the tissue with the greatest osmolality of the human body. Its outer portion is constantly exposed to an osmolality between 400-600 mosmol/kg of water, but its inner portion to more than 1.200.

Once the contrast is filtered at the glomerulus, it cannot be reabsorbed into the tubules because water is reabsorbed at that level; this encourages a gradual increase in the concentration of the contrasted medium in the tubules and thus, increases the osmolality of the intratubular fluid. The hyperosmolar direct damage of the renal tubular cells can occur as long as the intratubular fluid's osmolality exceeds the medullary environment[20].

Additionally, the osmolality and viscosity of the contrast media may aggravate the cytotoxic and vasoactive effect, and to induce the pathophysiological mechanism trigger, as hyperviscosity reduces the GFR and oxygenation at the medullar level, which favors a decrease of the urinary flow with the consequent retention of contrast at the kidney[19]. This effect occurs in greater or lesser amount in relation to the type of contrast medium employed[21], generating an imbalance between vasodilator and vasoconstrictor substances; this favors increasing the concentration of reactive oxygen species to entail reduction of nitric oxide, leading to endothelial dysfunction[22,23].

The cytotoxic effect of contrasting agents may be due to the action of the iodine they contain, which, due to the photolysis process, can be detached and generates high cytotoxicity[24]. Among the factors that induce photolysis are the storage time of contrast media and their exposure to light. Besides, specific properties of these contrast media, such as high osmolality, may increase the intrinsic cytotoxicity, such that the greater is the osmolality of a cellular medium, the greater the toxicity induced by iodine at a given concentration[25].

Regarding the pathophysiology of CIN it can be concluded that it is a very complex process and not entirely clear, which triggers an oxidative cascade that causes damage, cell apoptosis and inhibition of tubular reabsorption of protein, in addition to altering the balance of renal regulation vasodilatation-vasoconstriction that ultimately results in the loss of nephrons and tubules.

CONTRAST AGENTS

Contrasted agents used for these purposes contain iodine, which efficiently absorbs X-rays in the energy range of angiographic visualization. The monomeric ionic contrasts initially used were the hyperosmolar meglumine and diatrizoic acid sodium salts. These substances dissociate in cations and anions with iodine having a serum osmolality >1.500 mosmol/kg of water, therefore, because of their hypertonicity and their neutralization properties of calcium (forming chelates), many adverse reactions occurred; also, due to the availability of other less toxic contrasts, ionic are rarely used, although when ionic media are selected, it is necessary to take extra precautions to avoid complications.

Nonionic substances do not ionize in solution and provide more particles containing iodine per contrast milliliter than the ionic. Its osmolality re-

duces a lot (<850 mosmol/kg) because these substances exist in solution as single molecules and do not neutralize calcium; therefore they cause less adverse reactions[26].

The large multicenter studies have compared the first generation contrast media, the hyperosmolar (osmolality 1.000-2.500 mosmol/kg), with the second, low osmolality (400-800 mosmol/kg) and assert that the second has a lower risk of producing CIN over its predecessors. In fact, there is a direct correlation between the osmolality of a contrast medium and the appearance of CIN when this is >800 mosmol/kg[27]. It is important to mention that isosmolar contrasted solutions, of less toxicity, determine an increase in urine and plasma viscosity in relation to hyposmolar solutions[28], which has been widely documented in preclinical studies[29] and well hydrated patients[30].

The osmolality of the different contrast media has been the subject of numerous comparisons, on the other hand the volume of contrast used has been identified as an independent predictor of development of CIN, especially in patients with a history of previous kidney disease; however, there is not set a specific volume of maximum contrast, thus, it seems reasonable to limit, to the possible extent[31], the use of iodinated contrast in percutaneous coronary intervention (PCI) procedures.

URGENT PCI

In this context, the data regarding the CIN's incidence and predictor factors are scarce, since many studies that have evaluated them have excluded patients with acute myocardial infarction. In the substudy CADILLAC 2[32], the CIN's incidence was only of 4.6%, which may be due to the exclusion of patients with kidney disease or cardiogenic shock, as well as not having daily measurements of the renal function. In a group of patients with non-ST segment elevation acute coronary syndrome, it was significant the presence of: cardiogenic shock, diabetes mellitus, reperfusion time greater than 6 hours, anterior wall infarction, serum creatinine greater than 1.5 mg/dl and a serum urea greater than 50 mg/dl[33]; in another, there were identified as predictor elements of CIN: age over 75 years, the use of intra-aortic balloon pump, the location of an anterior infarction, the largest volume of contrast, and time to reperfusion[34].

PCI ON CHRONIC OCCLUSSIONS

The PCI on chronic total occlusions involves exposure to higher volumes of contrast, so that the risk of developing acute renal failure should be higher after this type of procedures. Despite this, the CIN's incidence and predictor factors in this context are little known, a fact that should encourage further studies[35].

PREVENTION STRATEGIES

Because there are no effective treatments once the CIN is established, prevention measures are vital[3]. Apparently, there are no substantial evidences, although there have been many trials and meta-analysis including antagonists of calcium, adenosine and endothelin, theophylline, N-acetylcysteine, prostaglandin analogs, L-arginine, statins, dopamine, natriuretic peptide, fenoldopam, hypertonic mannitol, iloprost, probucol and furosemide[3,18,36]. With the possible exception of N-acetylcysteine[37] at high doses, no treatment has been evaluated in several tests for CIN's prophylaxis. It is noteworthy that the nephroprotective role of N-acetylcysteine is attributed to direct antioxidant and vasodilator properties, and other indirect that could be related to the induction of hepatic glutathione synthesis[38]. Nevertheless, there is no clear scientific evidence on the dose to which should be used, which could be due to the vast heterogeneity of inclusion criteria and treatment of different studies, and in some instances, the guidelines of publications on the subject, that preclude a definitive gauging of the effectiveness of many prevention strategies; the same generally applies to the comparison among the hydration patterns[39], although their beneficial preprocedural effects are widely accepted and recommended in the guidelines for clinical practice[40], taking into account that dehydration is an individual risk factor for the CIN's development that can be avoided.

Furthermore, hypovolemia is an important substrate in the pathogenesis of CIN, as the volume depletion activates the renin-angiotensin-aldosterone system and vasopressin. Both, the angiotensin II and the vasopressin reduce the GFR mediated by their vasoconstrictor effect, worsening the medullary hypoperfusion and therefore the damage caused by the contrast[41]. This exposes the need to pre-hydrate the patient to ensure, *a posteriori,* an adequate filtration rate and to reduce the viscosity of the intra-

tubular fluid[18]. It has been suggested that bicarbonate solutions are superior to saline solutions, although this remains under discussion[42]. In the study REMEDIAL II[43], three hydration patterns were compared: a) with saline and acetylcysteine, b) with sodium bicarbonate, acetylcysteine and saline solution, and c) with ascorbic acid, acetylcysteine and saline solution; and it demonstrated that the incidence of CIN was significantly higher in patients randomized to saline solution in relation to those receiving sodium bicarbonate. Although in another study, there were no significant differences between two groups[44] of patients with CKD undergoing saline or bicarbonate solution, and the same pattern of acetylcysteine.

Diuretics have been evaluated for the prevention of CIN and initially, it was suggested that osmotics, such as mannitol, had a protective effect, but it could be seen in posterior studies that instead of a preventive effect, the contrary occurred because of its rebound effect, but combined with a glucose solution they have a protective effect, which increases urinary excretion rate and reduces substantially the viscosity of urine compared to saline regimen[45]. Loop diuretics have been associated with the occurrence of CIN, due to their action for increasing urinary excretion, along with the depletion of extracellular volume. However, when this effect is offset by additional volume, furosemide at low doses (0.25 mg/kg) seems to be effective in preventing CIN, because of the blockage it applies on the co-transport of sodium, potassium and chloride in the loop of Henle, which reduces the medullary hypoxia caused by contrast solution[46], as it was shown in two clinical trials in patients with pre-existing CKD[43,47].

The oral N-acetylcysteine with parenteral hydration[48] has also been used, as well as intravenous administration of vitamin E prior the procedure, which showed a more protective effect compared to placebo[49]; additionally, the ascorbic acid has demonstrated less nephroprotective effectiveness than high doses of N-acetylcysteine in patients with diabetes mellitus and CKD who underwent PCI[50].

Patti *et al.*[51] have studied the nephroprotective effect of statins in patients with PCI and found that the CIN's incidence was lower in the ones treated with these drugs. Nevertheless, this result cannot extrapolate to patients with GFR ≤ 40 ml/min/1.73m^2, as another study with 80 mg of atorvastatin administered two days before and after the procedure, along with a hydration pattern and N-acethylcysteine, did not show a reduction in the CIN's incidence[52]. On the other hand, Ozhan *et al.*[53] exposed that high doses of statins administrated together with N-acetylcysteine could be effective in the CIN's prophylaxis.

It seems obvious that the nephrotoxic drugs should be deleted previous days to PCI procedures, and included as drugs of risk, the nonsteroidal antiinflammatory drugs, loop diuretics or nephrotoxic antibiotics (aminoglycosides). In principle, the antihypertensive drugs from the group of inhibitors of the angiotensin converting enzyme are not contraindicated, thus their periprocedural use can remain. Metformin should be discontinued at least 48 hours before, because of the risk to induce lactic acidosis in the context of acute renal failure induced by contrast.

It is known that hemodialysis is an effective technique in terms of the capacity for rapid washing contrast in patients with CKD, but the results of four clinical trials to assess the benefit of prophylactic hemodialysis with respect to the usual measures offered conflicting results[3,54]. Hemofiltration is a technique that, prior to coronary angiography, has demonstrated to be effective in the prevention of CIN compared with a hydration pattern exclusively[55], so it has been suggested that this technique should be performed prior PCI and maintained for at least 12-18 hours after[56]; however, other studies are needed for its establishment as a prophylactic measure.

As it can be seen, there is no overall effectiveness of these measures, because there are especially controversial results. Among the ones with consensus today for preventing CIN and which have had better results are: appropriate homeostatic selection of the patient, hydration and use of the smallest possible volume of contrast media of low osmolality.

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