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EDITORIAL COMMENT

Contrast-induced nephropathy – an entity to bear in mind and to prevent: A nephrological perspective☆

Nefropatia induzida por contraste – uma entidade a considerar para prevenir – a perspetiva da nefrologia

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Contrast-induced nephropathy (CIN) is a frequently underdiagnosed entity that should always be borne in mind in clinical practice, since it has been identified as the third leading cause of acute renal failure in hospital settings.[1] One of the reasons for its high incidence is the large number of angiographic studies of various types performed for diagnostic and/or therapeutic purposes, including coronary interventions. Although in most cases CIN is reversible, it is associated with increased morbidity and prolonged length of hospital stay (and hence costs), as well as increased one-year mortality, even in patients who do not require dialysis. Its occurrence depends on procedure-related factors (contrast type, volume and osmolality) and on pre-existing risk factors, particularly age over 60 years, chronic renal failure and diabetes.[2]

It was initially believed that gadolinium-based contrast media would be safer than iodinated products, especially in patients with established chronic renal failure. However, subsequent experience and trials showed that these substances also have significant nephrotoxic effects, particularly with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2, and in addition lead to nephrogenic systemic fibrosis.[3]

In healthy individuals, iodinated contrast has a mean half-life of two hours and is virtually completely eliminated by the kidneys within 24 hours. The diverse pathophysiological mechanisms that cause CIN are the result of complex interactions between various factors. As well as the direct cytotoxicity of the contrast medium on tubular epithelial cells, there are also inflammatory and neurohormonal effects, including vasoconstriction of the medullary microcirculation resulting in severe ischemia.

CIN is defined as a rise in serum creatinine of ≥0.5 mg/dl or a 25% increase from baseline value, assessed 48-72 hours after the procedure.[4] Due to variability in patients' clinical status, its incidence is frequently underestimated, as it is usually insidious and only manifests from the third day after contrast administration.

In order to prevent CIN, it is essential to perform a careful assessment of the patient before any angiographic procedure. This may include risk stratification using risk scores,[5] in which evaluation of renal function is paramount, based not only on serum creatinine levels – which are influenced by non-renal factors including body mass index, age, gender and race – but, most importantly, on GFR, which is the best indicator of the kidneys' filtering capacity. The gold standard for measuring GFR is inulin clearance, but this cannot be applied routinely, and techniques based on urinary clearance of radioisotopes such as ^{125}I-iothalamate, ^{51}Cr-EDTA, or

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^{99}Tc-DTPA are not usually accessible in hospitals, and so in practice the measure used is estimated GFR (eGFR), calculated according to specially developed equations.

All these equations have limitations, with potential biases that need to be avoided by using the appropriate equation for a specific target population. After numerous studies evaluating their reliability for estimating GFR, there is general agreement that the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are currently the best for measuring eGFR in individuals aged over 18 years.[5] These two equations have been clearly demonstrated to be superior to the Cockcroft-Gault (CG) equation and to creatinine clearance based on 24-hour urine collection. Creatinine clearance should only be used when creatinine production is abnormal, such as in individuals with unusually high or low body surface area or muscle mass or whose diet has unusually high or low protein content.[6]

Despite their limitations, the MDRD equation has been validated in Caucasian and Afro-American individuals aged 18-70 years with chronic renal disease (eGFR <60 ml/min/1.73 m^2), while the CKD-EPI equation is more reliable for eGFR >60 ml/min/1.73 m^2. It should, however, be borne in mind that these equations should only be applied in individuals with stable renal function, not during acute episodes, and not in pregnant women or patients with severe comorbidities.[6,7]

Many publications, including the international guidelines, stress the value of serum measurement of cystatin C and its use for estimating GFR, since it is not affected by age, muscle mass, gender or protein intake. However, it is much more expensive to measure than creatinine.[7]

In the article by Nunes et al. published in this issue of the *Journal*,[8] the authors study a sizable sample of patients undergoing percutaneous coronary intervention and compare the ability of the CG and CKD-EPI equations to predict development of renal dysfunction following iodinated contrast administration. While focusing on the importance of determining eGFR, this work also highlights the underdiagnosis of renal dysfunction following the procedure. In addition, it stresses the importance of adopting elective methods for preventing CIN, not only related to the procedure itself but also by identifying groups at particular risk, such as patients with cardiovascular disease.

The authors performed a retrospective analysis of 140 patients of both genders, aged around 60 years, including blacks and non-blacks, with a wide range of body mass index and a variety of comorbidities, and at high metabolic and atherogenic risk. They did not use a single reference method for eGFR, but classified differences between the CG and CKD-EPI equations in obtaining the cutoff of 60 ml/min/1.73 m^2, which makes it difficult to draw conclusions. At the same time, given the clinical condition of the study population, it is highly likely that patients already had chronic renal disease before the procedure, which, as pointed out above, would mean the MDRD equation should preferably be applied, rather than comparing the CG and CKD-EPI equations. Moreover, for the same reasons, it is difficult to establish with any certainty the relationship between contrast administration and the existence of nephropathy in this vulnerable patient group without knowing the precise conditions under which the exam was performed. There are in fact several non-renal factors that are known to influence GFR in patients with acute coronary disease.

Despite the careful statistical analysis performed by the authors, stratification of the study population by age, eGFR and comorbidities would have provided valuable information on susceptibility to renal dysfunction as illustrated by the values given by the three equations (MDRD, CG and CKD-EPI) and on the actual incidence of CIN in patients undergoing coronary angiography.

The conclusions of the study by Nunes et al., in the context of this commentary, highlight above all the importance of systematically calculating eGFR before any procedure using iodinated contrast medium.

Conflicts of interest

The author has no conflicts of interest to declare.

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