



## EDITORIAL COMMENT

# Predicting contrast-induced nephropathy after percutaneous coronary intervention: Do we need formulas? A cardiological perspective<sup>☆</sup>



## Predição de nefropatia induzida pelo contraste após revascularização coronária percutânea: precisamos de fórmulas? – Uma perspetiva da cardiologia

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Contrast-induced nephropathy (CIN) features as an increasingly frequent diagnosis in the field of interventional cardiology. This is due to increased use of iodine-based contrast agents in cardiovascular diagnostic and therapeutic procedures performed in patients with multiple comorbidities, as well as in ever more complex clinical and angiographic settings that require lengthy or staged procedures.

CIN is estimated to be the third leading cause of renal failure among in-patients, accounting for 11-12% of cases.<sup>1</sup> According to some studies, its incidence can reach 25-30% in elderly patients, especially those with diabetes, ST-segment elevation acute coronary syndrome, left ventricular dysfunction or chronic renal failure (CRF). A subgroup at greater risk of developing CIN is those with concomitant diabetes and CRF.<sup>1</sup>

The European Society of Urogenital Radiology defines CIN as a transient elevation of >25% or an absolute increase of >0.5 mg/dl from baseline serum creatinine levels in the absence of an alternative etiology that was not present before contrast administration or is additional to previous abnormal levels. It generally begins 24-48 hours after contrast administration, serum creatinine reaching maximum levels in 3-5 days and returning to baseline within two weeks.<sup>2</sup>

Prognosis in CIN is poor, with high morbidity and mortality, prolonged hospital stay and increased risk for complications such as need for dialysis.

Although there have been improvements in detection and risk stratification, the pathophysiology and treatment of CIN are still largely undetermined. There appears to be agreement that prevention is the best form of treatment, mainly through intravenous hydration with normal saline (0.9%) before and after the procedure, and use of small quantities of low- or iso-osmolar contrast.<sup>1,3</sup>

Risk scores such as that developed by Mehran et al. can be useful, particularly in hospitalized patients and those with acute cardiovascular conditions, for predicting the risk of developing CIN, need for dialysis and mortality.<sup>4</sup>

Another issue is the usefulness of serum creatinine in isolation as a parameter to assess renal function; its low

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sensitivity means it is not a reliable marker. Glomerular filtration rate (GFR), which indicates the speed at which a volume of plasma is filtered by functioning nephrons, is a more accurate measure of renal dysfunction, since it may fall by 50% even though serum creatinine levels are still normal.

Various formulas have been developed to calculate GFR, notably Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), that consider not only serum creatinine but also other important variables such as age, gender, body weight and race. These mathematical formulas are only reliable in stable conditions, and the difference between two measurements should not differ by more than 10%, which generally does not occur in CIN.<sup>5</sup>

The first formula, that of Cockcroft-Gault (CG), was developed in 1973 using data from 249 men with creatinine clearance from 30 to 130 ml/m<sup>2</sup>. Its disadvantages are that it is not adjusted for body surface area, and is less accurate for estimating renal function in obese and older individuals, and when using standardized creatinine values.<sup>5</sup>

The MDRD formula, proposed in 1999 based on data from 1628 patients with CRF and GFR from 5 to 90 ml/min/1.73 m<sup>2</sup>, is adjusted for body surface area and has been tested in different populations (blacks, Europeans and Asians), individuals with and without diabetes and with and without CRF, cardiac transplant recipients, and potential kidney donors. Although less accurate in individuals without renal dysfunction and in kidney donors, it is more reliable than CG and in 2005 was adapted for use with a standardized serum creatinine assay.<sup>5</sup>

The CKD-EPI formula is the most recent (2009), and is currently recommended by national and international nephrology societies. It was developed in over 8000 white and black individuals with diverse characteristics, including with and without renal disease, diabetes, and organ transplants, and ages between 18 and 97 years. It was validated in a separate cohort of over 3000 individuals from 16 separate studies, with GFR ranging from 2 to 200 ml/min/1.73 m<sup>2</sup> and ages ranging from 18 to 93 years. Advantages of the CKD-EPI formula are that it is adjusted to body surface area, and is as accurate as the MDRD formula in patients with CRF and GFR <60 ml/min/1.73 m<sup>2</sup>, and more accurate in those with GFR >60 ml/min/1.73 m<sup>2</sup>.<sup>5</sup>

It should be borne in mind that all these formulas for estimating GFR suffer from three limitations: they use serum creatinine as a marker of glomerular filtration; they are less accurate in patients with high GFR (>60 ml/min/1.73 m<sup>2</sup>); and they are of little use in non-stable situations in which serum creatinine, and hence GFR, is changing.<sup>5</sup>

In view of the above, the study by Nunes et al. published in this issue of the *Journal*<sup>6</sup> is noteworthy for bringing these issues to bear on clinical practice. The authors performed a retrospective analysis of data on 8046 patients who underwent percutaneous coronary intervention (PCI) over a five-year period and for whom serum creatinine values were available for calculation of GFR by the CG formula.<sup>6</sup>

Patients with GFR >60 ml/min/1.73 m<sup>2</sup> were divided into two groups, those who developed CIN and those who did not. GFR was then retrospectively calculated using the CKD-EPI formula before and after PCI in order to evaluate the ability of the latter to predict CIN in patients without apparent

renal dysfunction (GFR >60 ml/min/1.73 m<sup>2</sup>) according to the CG formula.

Two points are worthy of mention. The authors do not report the overall incidence of CIN in the study population, which would be of considerable clinical interest; and as the investigators point out, the group without CIN was much larger, necessitating a somewhat abstruse mathematical calculation in order to match the groups, the result of which was a final study population of 140 subjects (76 with CIN and 63 without).

In their results, the authors report that individuals who developed CIN had higher mean serum creatinine levels before the procedure, and tended to receive larger volumes of contrast with higher osmolality, than those without CIN.

With regard to calculation of GFR, the CKD-EPI formula generally produced lower values than CG, whether or not the individual developed CIN, reducing GFR to less than 60 ml/min/1.73 m<sup>2</sup> in around 10% of cases. On multivariate analysis, body weight and male gender were identified as predictors of GFR <60 ml/min/1.73 m<sup>2</sup> by the CKD-EPI formula.

Reports in the literature indicate that, for the same creatinine level, GFR can be very different when gender, age and race are included in the formula. This is due to greater muscle mass in blacks, younger individuals and men, all of which groups also produce larger quantities of creatinine. It would have been interesting if the authors had been able to analyze all of the more than 8000 patients undergoing PCI for whom creatinine measurements were available at their tertiary center, as this would have contributed to the quantity and quality of knowledge in this area.

The variables identified as protecting against CIN were use of low-osmolar contrast agents and GFR >60 ml/min/1.73 m<sup>2</sup>, in agreement with the literature.

Hopefully, on the basis of this hypothesis-generating retrospective study with a small study sample, the authors will be encouraged to continue with this line of research by applying the formulas prospectively and validating them in the entire population of patients undergoing diagnostic and therapeutic procedures in their department.

In conclusion, perhaps the most important message of this analysis of CIN is that, whichever formula is most accurate for calculating GFR and hence obtaining a reliable assessment of renal function, it is essential to improve observation of patients, taking into consideration age, risk factors, comorbidities and current clinical status when deciding on the need for ever more complex diagnostic and therapeutic procedures that do not always improve cardiovascular health or prolong survival. When such procedures are deemed necessary, physicians can use risk models to predict the development of CIN, inform patients and their families of the risks involved, and implement well-known existing measures – periprocedural intravenous hydration and use of small volumes of low- or iso-osmolar contrast – to reduce the likelihood of CIN and its negative prognostic impact.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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