Contrast-induced nephropathy: the sin of primary percutaneous coronary intervention?

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This editorial refers to ‘Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy’, by A. Narula et al., on page 1533

Contrast-induced nephropathy (CIN) also described at acute kidney injury (AKI) is an acute renal failure occurring within the days after exposure to intravascular radiographic contrast material that is not attributable to other causes. It is the third most common cause of hospital-acquired renal failure, after decreased renal perfusion and use of nephrotoxic medications.1

More than 70 years after the first description of a fatal renal function impairment following the use of radiographic contrast media,2 CIN still represents a major and unmet clinical challenge, as this potential complication is associated with a prolonged hospitalization stay, a higher hospitalization cost, and a significant increase in morbidity and mortality.3,4 Unfortunately, after many years of research, the mechanisms of CIN remain poorly understood, although several mechanisms were identified, revealing a complex multifactorial pathophysiology with a high interindividual variability of the nephrotoxic effect of contrast media. Indeed, it is speculated that CIN might occur mostly in patients with pre-existing vulnerability of the renal medullary circulation, in response to stimuli disrupting the balance between the high metabolic needs of the tubular segments of the renal medulla and their hypoxic environment. In patients presenting with an acute ST-segment elevation myocardial infarction (STEMI) and treated with primary percutaneous coronary intervention (PCI), the situation becomes even more complex as we have, in addition to the toxicity of contrast media, a clinical situation mixing a high thrombogenic state, a burst of inflammation due to the myocardial damage, and a potential decrease in blood flow to the kidneys through vasoconstriction or haemodynamic instability (see Figure 1).

The most common manifestation of CIN is an asymptomatic transient decline in renal function that can be measured within 24 h of contrast media administration, and it usually peaks within 3–5 days, and returns to baseline within 10–14 days. Oliguric acute renal failure requiring haemodialysis can also occur, with longer resolution, and only a minority of patients who do not respond to conservative treatment will require permanent dialysis or kidney transplantation.5

Several risk factors for CIN have been identified; some are associated with pre-existing kidney vulnerability (chronic kidney disease, age, diabetes), some are due to the clinical situation (hypoxia, anaemia, heart failure, haemodynamic instability), and some are due directly to the toxicity of contrast media (type of contrast used and the volume of contrast injected). These risk factors have been integrated into risk scores to identify patients at high risk of CIN and subsequently at high risk of mortality.6,7

Among cardiac patients undergoing PCI, CIN ranges from 1% to 50%, with the highest rates in diabetic patients with previous renal impairment.8,9 The incidence of CIN varies depending on the clinical setting of the procedure, the population evaluated, and the definition used for CIN. In the absence of consensus from international societies of cardiology or nephrology, several definitions of CIN have been used in the literature, with an arbitrary range of thresholds sometimes expressed as an absolute increase in values of creatinine (from 0.3 to 2.0 mg/dL) or by a relative increase as compared with the baseline value (from 25% to 50%).8,10 A higher cut-off seems to be restrictive and less sensitive for predicting the incidence of CIN,11 and it has been argued that a low increment of change of serum creatinine levels corresponds to a significant drop in glomerular filtration rate (GFR) independently associated with higher mortality rates.3

Although it would seem logical to have a definition based on the decrease of GFR estimated with the Cockcroft–Gault or the MDRD (Modification of Diet in Renal Disease) formula, the most classic and accepted definition is either an increase in serum creatinine >0.5 mg/dL or 25% above the basal value within 48 h of contrast media administration. This definition has been validated and has established CIN as a major risk factor for mortality.6,7

The strong clinical impact of CIN is puzzling. On one hand, it is easy to conceive that the few patients undergoing dialysis or patients with
permanent worsening of their renal function caused by a CIN will have altered their prognosis with chronic kidney disease. On the other hand, it is surprising to see how a transient and asymptomatic decrease in GFR, with total recovery within a week, can be associated with a dramatic increase in mortality. The work of Narula et al. is a perfect representation of how CIN can affect short- but also long-term prognosis of patients after a diagnostic and therapeutic intervention requiring contrast media. Indeed, in their work, the 16.1% of patients developing CIN had an 8.0% mortality rate at 30 days and a 16.2% rate at 3 years as compared with the 0.9% and 4.5% mortality rates at 30 days and 3 years, respectively, for patients without CIN. When considering a broader clinical endpoint such as NACE (net adverse cardiac events), i.e. a combination of major bleeding and ischemic major adverse cardiac events (MACE), the increase is even more impressive, with 22.0% of events at 30 days and 40.3% at 3 years for patients with CIN when it was only 9.3% at 30 days and 24.6% at 3 years for patients who did not develop a CIN. The development of a CIN seems therefore to be a major event after PCI and an excellent risk factor to identify clearly patients at very high risk of major recurrent events.

Several characteristics of this analysis of the impact of CIN after PCI need to be considered thoughtfully. First the randomized nature of the HORIZONS trial has many advantages, among them the robustness of the data, the control of endpoints by an independent committee, and the quality of the follow-up, leading to strong evidence for such post-hoc analysis. Unfortunately, there are also some limitations and, despite the high quality of the data, we can notice that only 82.4% of patients had both a baseline and a follow-up creatinine measurement enabling the diagnosis of CIN and inclusion in the study. Are the missing patients even more at risk or dead? We can also imagine how much lower the rate of serial measurement of creatinine is in real life, and how it may reflect a lack of interest in the detection of CIN after PCI. The second limitation of this analysis is the selection bias towards patients with haemodynamic instability or cardiogenic shock inherent in exclusion criteria and in obtaining informed consent in a population of STEMI patients. In the analysis of Narula et al., there were almost no STEMI patients with cardiogenic shock (0.7%), whereas recent registries consistently find a rate ranging from 5% to 10% when all-comers are considered. However, an intra-aortic balloon pump was used more frequently in patients developing AKI (11.1%) than in those without AKI (4.5%), confirming that in STEMI haemodynamic and/or ischaemic compromise is likely to play an additive role in the occurrence of CIN on top of the specific toxicity of contrast media. Here again, we can only extrapolate the
real incidence of CIN in an unselected STEMI population and the prognosis associated with CIN when adding this subgroup of patients that bear most of the mortality burden. Another missing element is the distinction in prognosis in patients having complete recovery of their renal function and those who will lose some renal capacity or end up on dialysis.

Thanks to studies like that of Narula et al., data are accumulating on this frequent and serious complication of primary PCI. Unfortunately, we still do not know if CIN is a risk marker of the disease, of the frailty of the patient, of the treatment applied, or of a combination of all these taken together. Now, the next step in the field would be to focus more efforts on decreasing the incidence of CIN by applying potential preventive strategies. In STEMI, the challenge would be to identify such patients as a matter of urgency, and try to avoid the induced AKI before, during, and after the exposure to contrast media with prophylactic therapy or strategy. Prevention strategies in this clinical setting should focus on what we know. First, the kidney should be protected from contrast- or ischaemia-induced injury through adequate periprocedural hydration in order to enhance blood flow through the nephron. This could be done with an adequate periprocedural hydration protocol using saline or bicarbonates, and could even be started in a systematic fashion during transfer for primary PCI; such a strategy would need to be validated in a clinical trial. Secondly, the use of medication such as diuretics or angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) should be limited whenever possible in the periprocedural period. These drugs are used too often in the acute setting without much impact during the early days of MI. Thirdly, limiting the nephrotoxicity and amount of contrast administered should be kept in mind at all times, although, in this emergency situation, where the life (or the heart) of the patient is at stake, interventionists mostly have the objective of a fast and high quality procedure to re-open the culprit artery, often outweighing the risk associated with the use of a high volume of contrast. In fact, only very few studies have reported the average amount of contrast used in primary PCI which seems to be higher than in elective PCI, ranging between 220 and 280 mL. Finally, therapies focusing on countering vasoconstriction or providing protection against injury by oxygen free radicals still need to be found and tested in robust clinical trials to avoid discrepancies such as that found in randomized trials using a high intravenous dose of N-acetylcysteine in STEMI patients treated with primary PCI, with both positive and negative findings when hydration and limitation of contrast were used.

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