Pitfall in nephrology: contrast nephropathy has to be differentiated from renal damage due to atheroembolic disease

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ABSTRACT

Introduction: The topic of contrast-induced nephropathy (CIN) has been receiving an enormous amount of interest in recent times; however, this review is not a review of what CIN is, but what it is not. Methods: We will review the main topics demonstrating that the post hoc ergo propter hoc assumption that renal impairment occurring after contrast medium (CM) infusion is necessarily because of it, is wrong, as we are dealing with different diseases, depending on the way the CM is administered and on the type of patient. Results: After >1,000 often repetitive papers, we must deal with an unacceptably wide range of incidences of CIN, with completely different prognoses and astonishingly conflicting results regarding the efficacy of preventive measures with the exception of hydration. So what went wrong? How to separate tares from wheat? When years ago we challenged the diagnosis of CIN, the words cholesterol embolism had never appeared in this setting. Now, we can split the possible renal dysfunctions following CM administration into CM-related hemodynamic and/or tubular damage, cholesterol embolism, ischemia from acute blood loss or hypotension/hypoperfusion and nephrotoxicity from concomitant drugs. Conclusions: In a setting regarding millions of patients and millions of dollars/year, in order to clarify the true renal damage directly related to CM, we ask for prospective studies differentiating cohorts receiving intravenous and intra-arterial, transradial and transfemoral injections, and clinically relevant renal outcomes, thus avoiding the dangers that can come from the idolatry of a surrogate end point such an asymptomatic 25% transient increase of serum creatinine. To avoid that, patients may lose the possibility of a more useful radiological diagnosis, because of an exaggerated suspicion of risk.

Key words: Atheroembolic disease, Contrast-induced nephropathy, Iodinated contrast media, Renal cholesterol embolism

INTRODUCTION

The topic of contrast-induced nephropathy (CIN) has been receiving an enormous amount of interest in recent times. As to why we are writing on CIN for the umpteenth time, let we start by clarifying that this is not a review on what CIN is, but on what it is not. Therefore, we will review the robust reasons for which the term CIN has to be modified from a nephrological point of view.

DEFINITION OF CIN

What does CIN mean? Many people have answered that it is a kind of renal dysfunction that occurs following the use of iodinated contrast media, usually diagnosed on the basis of a 25% elevation in serum creatinine, or an absolute increase of 0.5 mg/dL within 72 hours after iodinated contrast
medium injection, and that the most exciting news in this area is the recent proposal of changing the definition from CIN to contrast-induced acute kidney injury (CI-AKI) (1-3). However, this is not the case. In fact, this new proposal also repeats the same misleading assumption of post hoc ergo propter hoc: in other words, if a variable degree of renal impairment occurs after iodinated contrast medium infusions, it does not mean that it occurs only because of that iodinated contrast medium infusion. Great confusion may derive from the wrong assumption that any kind of renal deterioration following maneuvers including the administration of contrast media should simply be identified as the same entity that is contrast nephropathy, similar in pathogenesis and, therefore, prevention and treatment. We are dealing with completely different diseases, depending on the way contrast media are administered and on the type of patient.

WIDELY DIFFERING INCIDENCE OF SO-CALLED CIN

After years of often repetitive papers (about 1,000 in most recent times, only <5% of them original articles), many thoughts are troubling (4-7). First of all, the incidence of CIN has been reported in an unacceptably wide range: from 1%-2% (with 0.4% requiring dialysis) to 33% (with >5% requiring dialysis). It is difficult to accept that the same disease has such wildly different clinical phenotypes.

Luckily, more recent studies conducted only in a subset of people who only underwent contrast-enhanced computed tomography have demonstrated the absence of any clinically relevant renal involvement (8-14), thus leading some authors to conclude that, in the words of Katzberg and Ne-whoise (15), renal impairment after intra-arterial or intrave- nous injection of iodinated contrast media has been “unjustifiably equated,” and “the incidence of CIN with intravenous administration of contrast media has been overstated … because of the extrapolation of the cardiology experience with percutaneous catheterization, ventriculography, and coronary intervention” (15).

Another interesting observation by the same authors was that an impressive increase in the occurrence of CIN has been recorded mainly in the cardiology literature and subsequent to the period in which cardiac catheterization became frequent (the mid-1970s), while the case for renal impairment following intravenous injection was rare, if ever made, even if high osmolar contrast media were the only ones available up to the early 1980s. Furthermore, the authors stress the difference in incidence of serious outcomes with renal damage needing dialysis and death in patients who have undergone intra-arterial procedures (up to 7% for dialysis and 13.9% for death, as compared with zero dialysis and zero death in patients who have undergone contrast-enhanced computed tomography even with renal insufficiency). The authors also underscore the fact that patients who have undergone diagnostic or therapeutic coronary angiography have more than one strike against their kidneys: they suffer also from multiple comorbidities such as vasculopathy and hemodynamic instability eventually leading to ischemic episodes or the need for potentially nephrotoxic drugs, and may have undergone emergency procedures, and suffered from peri-procedural shock, congestive heart failure, cardio-ac infarction or liver disease (15). Furthermore, recent paper have also clearly demonstrated that, in the setting of intra-arterial procedures, the role of anemia consequent to post-procedural bleeding is an increased independent risk factor for renal impairment (16, 17).

Lastly, in the last few months there is a growing perception that, within the setting of intra-arterial procedures, there is a different risk factor for renal involvement when using radial or femoral access, with femoral access leading to the greatest risk because of its proximity to the high flow bed of the renal arteries (18-31).

THE SPECTRUM OF POSSIBLE CLINICAL ENTITIES TO BE ENCLOSED WITH THE SO-CALLED CIN

First of all, there has been a challenge to the concept that a small increase in serum creatinine should always have a clinical pathological meaning, as it can also occur as a spontaneous fluctuation, with clear implications from studies assessing random variations in renal function (32). Furthermore, it has been argued that a “distressingly small number of these studies have included control subjects,” while a small increase in serum creatinine which reached the threshold accepted for a diagnosis of CIN has been demonstrated also in 32,161 patients hospitalized for coronary problems who did not undergo iodinated contrast medium injection (15, 33).

On these bases, we can summarize all of the possible clinical entities occurring when patients undergo iodinated contrast medium injection that can induce renal impairment, dependent on, or independent of, the contrast medium by itself (Fig. 1).

When contrast media are introduced into the venous bed (as when performing computed tomography) renal failure may really be a mere consequence of damage by contrast agents, including alterations in renal hemodynamics, rheological properties, adenosine, endothelin, reactive oxygen species or direct cytotoxic effects on renal tubular cells, so that large volumes of contrast media are crucial factors for
renal damage. The histological pattern would be that of renal tubular injury due to direct or mediated toxicity to tubular brush-border and intracellular components following trans-tubular traffic and medullary ischemia (Fig. 2).

When contrast media are introduced into the arterial vascular bed, renal dysfunctions following such procedures may be due to other reasons than contrast exposure alone. The most important “competitor strike” is renal damage from embolism of cholesterol debris due to catheter manipulation in the abdominal aorta (Fig. 3). This is an often undiagnosed condition that may occur even in the absence of overt clinical symptoms such as blue toes, livedo, hypereosinophilia and complement consumption. In this last case, renal damage follows the mechanical occlusion of the renal arterial bed with cholesterol crystals (Fig. 4) that are dislodged from atheromatous plaques of the aorta and other major arteries after intravascular trauma with angiographic catheters during invasive vascular procedures, and the role of the contrast medium is marginal, if there is any.

Seven years ago, we challenged the diagnosis of CIN, stressing that sentences such as “contrast nephropathy is a recognized renal complication following coronary angioplasty” (2) may be completely misleading, as we cannot be sure that renal dysfunction after coronary angiography is explained by contrast nephropathy alone in this setting as well (34). We commented on the worrying and misleading statements on this topic underscoring the need for a differential diagnosis with other causes of renal impairment, including cholesterol crystal embolisms, that had never been considered in this setting at that time.

In the years since then, the term cholesterol embolism has actually sometimes appeared in the literature, and the possibility of “other cause of renal failure (such as atheroemboli) following intra-arterial administration of contrast-medium” (33, 34) or the fact that the diagnosis has to be made after excluding other causes of renal damage is sporadically quoted in a few papers. But it is not enough. Most authors still write on CIN as a unique pathological entity always correlated to type, amount and characteristics of contrast media, and meta-analyses and studies continue to consider patients all together, whatever the settings in which the iodinated contrast media are injected.

Fortunately, some clear milestones have been reached in the last few years.

Therefore, by splitting the types of renal dysfunction that may follow (not necessarily be due to) iodinated contrast media injection, we can see that only 2 stairs of the pyramid (the gray ones) are causally linked to contrast media, while cholesterol embolism and acute blood loss are only caused by intra-arterial injection, and lastly the other potential strikes for renal function may be shared with hospitalized people not using contrast media – i.e., other comorbidities, hemodynamic instability, ischemic episodes, shock and need for potentially nephrotoxic drugs.

Central to the pathophysiology of renal dysfunction causally due to iodinated contrast media are alterations in renal hemodynamics, rheological properties, endocrine and paracrine factors (adenosine, endothelin and reactive oxygen species), hyperosmolar and hyperviscous alterations of intratubular fluids, direct cytotoxic effects on renal tubular cells consequent to large volumes of contrast media. On the other side, in the case of atheroembolic renal disease, the renal parenchyma is mechanically damaged by cholesterol crystals. In fact, kidney is usually involved because of the proximity of the renal arteries to the abdominal aorta, and the enormous amount of blood flow through it; therefore, where the erosion of atheromatous plaque has occurred, renal parenchyma becomes a prime target in cholesterol crystal embolization, eventually leading to intra-arterial, arterial or glomerular mechanical obstruction.

If we look at the anatomical pictures of this kind of renal damage, we can easily understand way it may progress to chronic irreversible renal failure (Fig. 4) (35), while the progression of only hemodynamic damage or even acute ischemic tubular damage such as that attributable to contrast media, toward an irreversible end-stage renal disease, would be much less explicable – nephrologically speaking. In fact, it has been argued also that CIN by itself might be a

![Image](https://via.placeholder.com/284)
Fig. 2 - When iodinated contrast medium is introduced into the venous bed, as when performing computed tomography (A-C), renal damage may merely result from contrast-induced mechanisms of damage (D), such as blood flow and tubular flow alterations and direct iodine-related cellular toxicity, with a histological pattern confined to tubular injury (E).

Fig. 3 - When contrast medium is introduced into the arterial vascular bed (A, B), renal dysfunction may result from other factors than mere contrast exposure, among which cholesterol embolism is the most important “competitor strike” (C, D).

progression factor for worsening renal and systemic prognosis (36-38). However, as it is clear that patients with CIN had more comorbidities at the time of contrast medium administration than did patients without CIN and that these multiple comorbidities may be independent causes of CIN, it seems many times more likely that CIN is a marker of worse prognosis. Furthermore, “why should CIN by itself be able to cause death or other serious complications?” (15).

On the other hand, atheroembolic renal disease, also called atheroembolism, cholesterol embolism, cholesterol athero-
Atheroembolic renal disease or cholesterol crystal embolization, is often an underdiagnosed renal illness, as well as an underdiagnosed systemic disease. In fact, cholesterol crystals that are dislodged from atheromatous plaques of the aorta and other major arteries, spontaneously or during thrombolytic/anticoagulant therapy or after intravascular trauma with angiographic catheters, may reach other vascular beds (in gut, skin, upper and lower extremities) and trigger inflammatory responses with the appearance of livedo reticularis, purple toes syndrome and retinal emboli, while eosinophilia and serum complement consumption can be detected. Many difficulties have been reported in diagnosing atheroembolic disease, which therefore has been labeled as the great masquerader. Its precise diagnosis can be made only by demonstrating the cholesterol crystals in retinal examination or in skin biopsy or within the renal vessels and glomeruli in kidney biopsy (or nephrectomy or autopsy) specimens. Because of the difficulties in the diagnosis, the exact incidence of atheroembolic renal disease is not known, and also for this clinical entity, the reported ranges are unacceptably wide (in autopsy studies, from 4% in elderly subjects aged 65 years and older who had minimal atherosclerosis, to 77% in older patients with severe atherosclerosis; in clinical studies, up to >12% of cases following coronary angioplasty) (39-42).

**Prevention of the so-called CIN**

Prognosis of the so-called CIN has been described in a completely different way, from cases in which the only remark is a transient very mild increase in serum creatinine without clinical meaning, to cases associated with an increased rate of morbidity and mortality with death of kidney and patients, days of hospitalization and health costs. Furthermore, the enormous body of reviews and meta-analyses devoted to analyzing the relatively small number of studies looking for preventive strategies able to avoid or reduce the deterioration of renal function following administration of contrast agents, did lead to astonishingly conflicting results on the efficacy of bicarbonate, infusion, diuretics, antioxidant renal vasodilators, vasomotor agents and also types of contrast medium in respect to osmolality, lower osmolar versus so-osmolar. In particular, while agreement does exist only on the protective role of volume infusion and the worsening effect of diuretics, controversial data are reported on the role of N-acetylcysteine (NAC), a molecule with antioxidant properties, that has been described as able to significantly reduce, or to reduce only in patients with preexisting renal diseases, or to reduce only at a borderline level of statistical significance or not to reduce at all, the incidence of contrast nephropathy after administration of contrast media. The same is true for bicarbonate infusion, associated with protective, null or worsening effects on clinical outcome of CIN (43-58). The most probable explanation for such an unacceptable muddle and muddling of conclusions is that so-called CIN is not a single disease, but a constellation of different clinical entities. So what went wrong? How to separate tares from wheat?

The largely recognized efficacy of volume infusion is likely to be applied to the direct pathogenic mechanisms of the true CIN. In fact, volume infusion before injection of iodinated contrast media will reduce the contact time between iodinated contrast media and endothelial cells, thus reducing direct cytotoxicity, and will avoid tissue hypoperfusion and hypoxia aggravating cellular damage that follows vasoconstriction and reduction in medullary flow consequent to hyperviscous contrast media. Furthermore, volume expansion after injection of iodinated contrast media will avoid homocentrization due to hyperosmotic diuresis, and tubular obstruction due to glomerular filtration of hyperviscous iodinated contrast media, thus blunting the tubular-glomerular feedback responsible for prolonged glomerular vasoconstriction (59, 60).

**Conclusions**

We are dealing with a topic regarding millions of patients and millions of dollars: some time ago, a decade ago, a number of 80 million doses of iodinated intravascular contrast media was registered in only 1 year. In the last few decades, the use of contrast-enhanced computed tomog-
raphy and cardiac catheterization has increased roughly by 800% and 400%, respectively, and generally speaking, diagnostic imaging is a US $100 billion a year industry in the United States. If we consider that the number of patients who have undergone cardiac catheterization is increasing, incidence of chronic renal failure and diabetes are increasing and life expectancy is increasing, the exposure to a risk for renal dysfunction following contrast media injection will be unavoidably increasing.

Therefore it is pivotal that we clarify the boundaries for true renal damage only directly related to iodinated contrast media, to avoid having patients lose the possibility of a more precise and useful diagnosis because of an exaggerated, vague and generic suspicion of risk.

Tired of the same old studies, review and meta-analyses collecting nonhomogeneous studies for what concerns different ways of administration of contrast media, different clinical settings and different risk factors for renal damage, we ask for separate prospective studies and separate meta-analyses for “renal dysfunction after intra-arterial angiography only” and “renal dysfunction after intravenous contrast media administration only,” as also requested from other authors in unrecognized papers some years ago (59), and further ask for studies that will separately analyze transradial and transfemoral access.

Furthermore, we completely agree with previous studies strongly suggesting that more hard clinical outcome measures have to be established in future clinical trials to clarify the true incidence of a clinically relevant renal damage following iodinated contrast media injection, to avoid dangers that can come from the idolatry of a surrogate end point such a 25% transient increase of serum creatinine (15, 33).

Let us conclude with the sentence of another author: “We believe that the risk of CIN with CE CT [computed tomography] is overstated and that a more accurate assessment of the risk of CIN could lead to wider CM [contrast medium] use, more accurate diagnoses, and better clinical treatment” (15).

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