

## Contrast-Induced Nephropathy: Contrast Material Not Required?

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**OBJECTIVE.** This commentary deals with the study by Newhouse and colleagues in this issue of the *AJR* discussing the implications of a lack of a control group in previously published studies on contrast-induced nephropathy (CIN).

**CONCLUSION.** Until more rigorous studies including an appropriate control group address the issue of CIN, our understanding of the actual risk of CIN when administering IV contrast media is limited.

**P**erforming a literature search on the term “contrast-induced nephropathy” (CIN) returns numerous articles about studies based on the premise that presupposes the existence of CIN. These studies define risk factors for CIN [1–3], test medications and hydration regimens to reduce the incidence of CIN [4–11], and compare the incidence of CIN using various contrast agents [12–19]. In addition to single trials, results from multiple studies have been compiled into reviews and meta-analyses for those who prefer “one-source” summations [20–23]. Most of the studies in the literature have focused on patients undergoing angiography (coronary or noncoronary, with a large subset evaluating coronary angioplasty patients), but few articles report on populations undergoing CT and therefore IV administration—not intraarterial administration—of contrast media [18, 24, 25]. Furthermore, a few investigators have performed studies to determine how to simplify the identification of patients considered at risk for CIN to obviate a screening creatinine level in all patients undergoing a contrast-enhanced study [26–28].

But what if this premise is all wrong? What if there is no such entity as CIN? Or, more likely, what if the incidence of CIN is so low that the health risk is greatly smaller than assumed? What if there is no real increase in serum creatinine level in the general population that can be attributed to the intravascular administration of contrast media?

This concept is raised in the article “Frequency of Serum Creatinine Changes in

the Absence of Iodinated Contrast Material: Implications for Studies of Contrast Nephrotoxicity” by Newhouse et al. [29] published in this issue of the *American Journal of Roentgenology*. In their study, Newhouse and colleagues take a novel approach to the issue: What if the incidence (and existence) of CIN (or as they call it “postcontrast creatinine increase”) is overestimated because no studies have looked at the background noise? That is, what if no studies have accounted for the fluctuation that occurs in creatinine levels over the course of several days for as yet undefined (and probably multiple) reasons? What if a large proportion of the increase in creatinine that occurs in some patients is due to some other combination of factors and would have occurred whether or not iodinated contrast medium was administered?

In a review of the literature on the nephrotoxicity of IV-administered contrast media, Rao and Newhouse [30] found two small series that tried to address this point. Admittedly, both studies are small and are perhaps not powered to find a difference in the incidence of renal impairment if one were truly present. The first article was published in 1985 and describes a study performed by Cramer et al. [31]. In that prospective study of 193 patients undergoing contrast-enhanced CT of the brain and 233 control subjects who underwent CT of the brain without contrast media, there was no difference in the rate of renal impairment (defined as a creatinine increase of 50% over baseline to above normal) in the patients

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versus the control subjects. In the highest risk group studied—those with a creatinine value of  $\geq 1.5$  mg/dL—no renal dysfunction occurred in the patients exposed to contrast material but did occur in two patients who did not receive contrast material.

The second series, reported by Heller et al. [32] in 1991, defined renal impairment as a serum creatinine increase of 50% above the baseline value or an increase of 0.04 mmol/L; those authors compared 479 patients with 405 control subjects. In the control group, 4% developed renal impairment, which did not differ from the group receiving high-osmolality contrast medium (HOCM; also 4%). There was a difference between control subjects and patients receiving low-osmolality contrast medium (LOCM); in the latter, the rate of renal impairment was 12%. The authors explained that because the assignment of contrast type was nonrandom, it was likely that the sicker patients received LOCM; they further supported this claim by showing a higher overall mortality rate among those who received LOCM (12.3%) than those receiving no contrast material (6.2%) or those receiving HOCM (4.1%). Furthermore, the authors included a case control study of the 51 patients who developed renal impairment compared with a control group of 150 patients who received contrast material but did not develop renal impairment. Members of the control group were less likely to have undergone surgery or to have had a blood transfusion. They concluded that these extenuating circumstances—for example, hypotensive renal damage from blood loss—were thought to explain the higher rate of renal impairment. Heller et al. concluded that “fear of causing or exacerbating renal damage should not be a reason” to withhold contrast media.

A more recent study presented at the Society of Uroradiology 2008 Annual Meeting by Bruce and Pozniak [33] compared changes in serum creatinine levels between recipients of IV iodinated contrast media for CT and control subjects. A total of 15,357 patient observations were included: 594 patients received iodixanol, 5,939 received iohexol, and 8,824 unmatched control subjects received no contrast material. The results of their study showed no difference in the rate of renal dysfunction (defined as an increase in creatinine of 25% over the baseline value or an absolute increase of 0.5 mg/dL) in those who received contrast media versus those who did not when creatinine level was  $\leq 1.5$  mg/dL

(4.4% vs 4.2%, respectively). In the group whose creatinine level was between 1.6 and 2.5 mg/dL, 22% of those who received contrast media had CIN, whereas 11% of those who did not receive contrast media had “CIN” ( $p = 0.04$ ). Bruce and Pozniak concluded that there was a high rate of “CIN” even in patients who did not receive contrast media and stated that much of the toxicity ascribed to contrast media was likely due to underlying medical conditions (“hospital-induced nephropathy”).

Newhouse and colleagues [29] lend support to the notion of “hospital-induced nephropathy.” In their article, the authors report on a population of 32,161 patients with a creatinine level drawn for 5 consecutive days who did not undergo contrast administration for the 10 days preceding the available creatinine levels or during the 5 days of observation. In this control group, the average creatinine level was 1.65 mg/dL at baseline and 1.45 mg/dL on day 4. Of the patients with a baseline creatinine of 0.6 mg/dL or higher, 24% had a change in creatinine level that would have resulted in a diagnosis of CIN (defined as a change of at least 25% from baseline) if contrast material had been administered. (This is an average derived from the first line of Table 1 in their article.) Newhouse et al. conclude that without an appropriate control group, previously published series reporting a range of nephrotoxicity from contrast media administration of 0–76% may not accurately capture the nephrotoxic effects (or lack thereof) of contrast media administration.

Although the absence of control groups who did not receive contrast material in most studies makes it difficult to accurately assess the rate of CIN, it would be foolhardy to conclude that CIN does not exist, a point with which Newhouse et al. [29] concur. Contrast material is nephrotoxic in large doses in animal studies [34–36], and it is likely that some patients suffer renal damage from contrast media administration. However, it is clear that the risk of CIN has been overestimated by the failure to correct for the baseline occurrence of renal dysfunction in sick patients who do not receive contrast media. Furthermore, many other dogmas about CIN are called into question by the results reported by Newhouse et al. For example, preexisting renal impairment as shown by an elevated serum creatinine value has long been considered a risk factor for CIN based on studies in which patients with

a normal creatinine value served as control subjects and iodinated contrast material was administered to both groups. Newhouse et al. found in their study that a higher initial creatinine level in patients who do not receive contrast media leads to a greater chance that a given absolute change—say, an increase of 0.5 mg/dL, a common criterion for CIN—will be exceeded.

Although Newhouse et al. [29] raise substantial issues about CIN, the solution proposed—that “future experiments should have appropriate controls”—is easier said than done. It is impossible to randomize patients to contrast and no-contrast-administration groups. Meanwhile, selecting a matched control group is not easily accomplished. There are reasons some patients receive contrast media and others do not. It may be that patients who need contrast-enhanced imaging studies are more ill than those who do not, and yet there are some patients who do not receive contrast material specifically because they are too ill.

As another example of the difficulty of obtaining “appropriate controls,” consider this thought experiment. In general, patients receiving intraarterial contrast media have higher rates of postprocedure renal dysfunction than patients receiving IV contrast media. How much of this difference is explained simply by the route of contrast media administration versus other procedure-related factors is controversial. Assume three matched populations: One receives intraarterial contrast media; one receives IV contrast media; and one, the control group, receives no contrast media. These study groups are matched populations, but this study this is not a randomized study. What is the most likely result? There may be no difference in the rate of renal dysfunction between the patient group receiving IV contrast material and the control group or perhaps there is a small difference. Either way, the difference between the group receiving intraarterial contrast material and the control group is likely to be larger. Even after correcting for the rate of nephrotoxicity (“hospital-induced”) in the control group, it is plausible that the conclusion may be drawn that intraarterial administration of contrast media is more nephrotoxic than IV administration or alternately that intraarterial administration of iodinated contrast media is a cause of CIN. But what is the one factor that cannot possibly be matched or controlled for? It is the intraarterial procedure itself. It

## CIN: Contrast Material Not Required?

may be procedure-related atheromatous emboli or something else that damages the kidneys, but separating the relative contributions of these causes and the contrast media administration will be difficult. In addition, other factors that matching does not take into account may exist: Angina (leading to coronary arteriography) as a marker of the severity of atherosclerotic disease is just one possibility. Thus, using matched control groups, although better than using no control subjects, can go only so far in assessing CIN risk.

The fact that it will be difficult to achieve the authors' recommendations for the design of future CIN studies does not diminish the importance of the Newhouse et al. [29] study. The results of that study clearly show that there is some baseline level of nephropathy (or at least, of creatinine change) that occurs in sick patients who do not receive contrast media. To what degree we should discount the perceived risk of nephropathy from the administration of contrast media is not answered by this study because the patients evaluated are not matched against any population who received contrast media. Nevertheless, the bar has been raised for the design of future studies of CIN. Particularly with regard to IV administration of contrast media, we need better data on CIN risk stratified by the degree of preexisting renal impairment; this need is magnified by the increased complexity of medical imaging decision making caused by the news of nephrogenic systemic fibrosis (NSF) and its relationship to underlying renal insufficiency. Until we better understand CIN and NSF, we may be unnecessarily placing patients thought to be at risk for CIN at risk for NSF instead.

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## Baumgarten and Ellis

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### FOR YOUR INFORMATION

The reader's attention is directed to the article pertaining to this commentary, which appears on the preceding pages.