Pathogenesis of Contrast-Induced Nephropathy: Experimental and Clinical Observations with an Emphasis on the Role of Osmolality

Michael R. Rudnick, MD, FACP,* Stanley Goldfarb, MD, FACP†

*Division of Nephrology and †Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

Experimental studies suggest that the pathogenesis of contrast media nephrotopathy is due to a combination of renal ischemia and direct tubular epithelial cell toxicity. Clinical studies to date have demonstrated a reduction in clinical contrast nephropathy with the introduction of low-osmolar and, more recently, iso-osmolar contrast media. Numerous experimental studies have examined the role of osmolality per se in the pathogenesis of contrast nephropathy, with conflicting results. Whether iso-osmolar contrast media are the least nephrotoxic iodinated contrast media needs to be determined with large prospective randomized clinical trials.
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Key words: Contrast-induced nephropathy • Osmolality • Renal medulla

Intravascular administration of iodinated contrast media continues to be a common cause of hospital-acquired acute renal failure. Although the clinical presentation of contrast-induced nephropathy (CIN) has been well described, the exact pathogenetic mechanisms for this complication have not been completely elucidated. Clinical observations over the past two decades have demonstrated a reduction in the incidence of CIN with the introduction

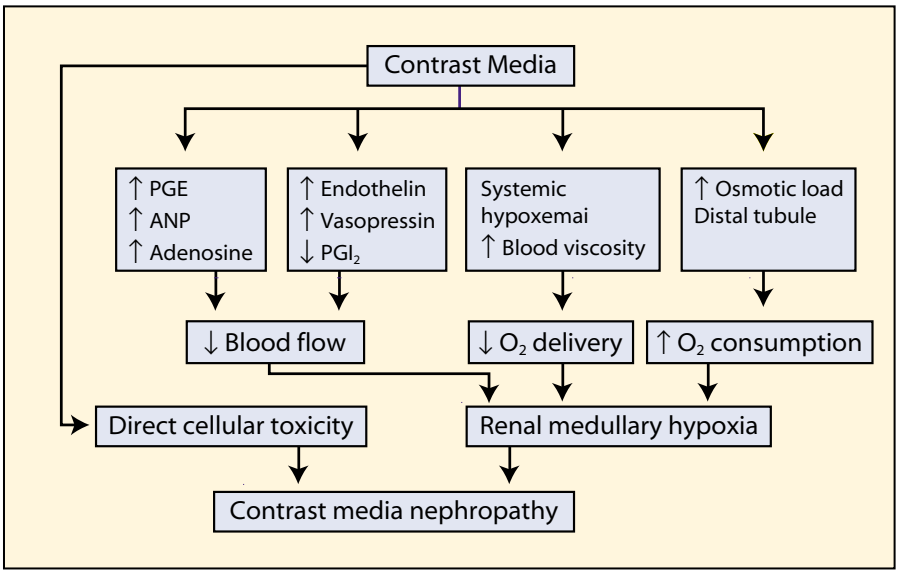

Figure 1. *Pathogenesis of contrast media nephropathy. ANP, atrial natriuretic peptide; PGE, prostaglandin E; PGI_2, prostaglandin I_2; ↑, increase; ↓, decrease. Adapted with permission from Heyman et al.*[5]

of low- and iso-osmolar contrast media. This review focuses on the experimental pathogenesis of CIN with an emphasis on the role of osmolality. The clinical evidence of decreased CIN with low-osmolar contrast media (LOCM) compared with high-osmolar contrast media (HOCM) is also discussed.

Pathogenesis

Renal Hemodynamics

It is currently believed that disturbances in renal hemodynamics and direct tubular epithelial cell toxicity by contrast media are the primary factors responsible for CIN (Figure 1). Early investigations into the pathogenesis of CIN demonstrated that after injection of HOCM, there is a transient increase followed by a more prolonged decrease in renal blood flow (RBF).[1,2]

The repeated demonstration of contrast-induced renal vasoconstriction is the basis for the hypothesis that renal ischemia is a major factor in the pathogenesis of CIN. Subsequent experiments in animal models of CIN have demonstrated that contrast media produce epithelial cell necrosis primarily in the area of the medullary thin ascending limb (mTAL).[3] These histologic changes were most pronounced in the outer medullary region of the kidney and correlated with the magnitude of disturbance in renal function.

Later studies directly measured medullary oxygen tension in a contrast nephropathy animal model and demonstrated that contrast media decreased medullary oxygen tension—an effect that was reversed with furosemide.[4] The renal medulla normally has an extremely low oxygen tension as a result of the countercurrent exchange of oxygen and the high transport activity of the mTAL.[5] The low oxygen tension in this area of the kidney makes it uniquely susceptible to ischemic injury from factors that may diminish blood flow or increase oxygen utilization.

Based on these observations, it was proposed and later demonstrated in animals that contrast media induce renal injury by worsening medullary hypoxia.[4,5] The mechanisms by which contrast media worsen medullary ischemia include contrast media–induced renal vasoconstriction with resulting diminished oxygen delivery (Figure 1). In addition, the solute diuresis produced by the hyperosmolality of contrast media may increase the transport work requirement in the mTAL, a process requiring oxygen utilization.[5]

These observations support the theory that contrast-induced medullary hypoxemia can be reversed with furosemide and simulated with mannitol.[4] Contrast media also have shown an ability to cause red blood cell aggregation, which can further impair oxygen delivery.[6] More recent studies suggest that the increased viscosity of iso-osmolar dimeric contrast media may worsen medullary hypoxemia.[7] A diminished transit time of the contrast media in the tubule (due to its higher viscosity) could lead to increased tubular pressures, which in turn can cause a decrease in glomerular filtration rate (GFR) and RBF by compression of peritubular vessels.[8] Another potential mechanism for this negative effect of viscosity is that a diminished tubular transit time could result in increased time for solute transport and thus increased oxygen utilization.

Clinical observations over the past two decades have demonstrated a reduction in the incidence of CIN with the introduction of low- and iso-osmolar contrast media.

Direct Cellular Toxicity

A direct toxic effect of contrast media on renal epithelial cells was initially suggested by contrast-induced pathologic changes, which included epithelial cell vacuolization, interstitial inflammation, and cellular necrosis[9,10] as well as increased enzymuria following contrast administration.[11] In addition, suspensions of proximal tubular epithelial cells exposed to diatrizoate demonstrated abnormalities in several markers of cellular injury; these effects were more pronounced by hypoxia and HOCM compared with LOCM.[12,13] More recently, an in vitro model of proximal and distal tubule monolayer cell cultures demonstrated an increase in cellular mortality with HOCM compared with LOCM.[14]

Role of Osmolality

Given the clinical observations that CIN in high-risk patients is less frequent with LOCM compared with HOCM (see below) and that iso-osmolar contrast media may be even less nephrotoxic than LOCM,[15] it is reasonable to question what role osmolality per se may have in the pathogenesis of contrast-induced renal injury.

In early studies, the renal effects of hypertonic solutions of saline or mannitol were compared with HOCM, such as diatrizoate. These studies demonstrated that these noncontrast hyperosmolar solutions were capable of causing renal vasoconstriction with reductions in RBF and GFR, impairing para-aminohippurate extraction, and producing enzymuria similar to HOCM, although these perturbations were often of a lesser magnitude than those seen with contrast media.[1,2,16,17] It has been proposed that these nonspecific effects of hyperosmolality could be caused by osmolar-driven solute diuresis with activation of tubuloglomerular feedback or an increase in tubular hydrostatic pressures, which may cause a compression of the intrarenal microcirculation and decreased GFR.[17]

In an in vitro model using a renal epithelial cell line, DNA fragmentation (a marker of apoptosis) was increased in cells exposed to HOCM and the degree of fragmentation was proportional to the osmolality of the contrast.[18] Solutions of mannitol and sodium chloride with osmolalities similar to the HOCM also caused DNA fragmentation, but to a lesser degree. This study indicated a direct cytotoxic effect of contrast media independent of hypoxia, which to a large extent may be related to hyperosmolality. In contrast, experiments in other in vitro models demonstrated that contrast media, but not equiosmolar mannitol, resulted in mitochondrial dysfunction, suggesting that the nephrotoxic effect of contrast media is related to some property other than osmolality.[19]

Subsequent experiments comparing the renal effects of iso-osmolar contrast media (iotrolan and iodixanol) with LOCM and HOCM have not demonstrated a reduction in renal abnormalities with the iso-osmolar contrast agents. In many of these studies, the iso-osmolar agents actually produced more nephrotoxic abnormalities than those seen with LOCM and HOCM, possibly because of their increased viscosity. Specifically, iso-osmolar contrast media have been reported to cause more proximal tubular cell vacuolization, red blood cell aggregation and cessation of flow in the renal microcirculation,[6] and reduction in RBF[20,21] compared with hyperosmolar contrast media. Iso-osmolar contrast media have also been demonstrated to cause a greater increase in tubular hydrostatic pressures and fall in single-nephron GFR compared with hyperosmolar contrast.[8,22] Iso-osmolar contrast media have been shown to decrease medullary oxygen tension to the same degree as LOCM, arguing against the proposal that part of the reduction in oxygen tension in the outer medulla following contrast exposure is due to increased transport work caused by an osmotic diuresis.[23]

Given the clinical observations that CIN in high-risk patients is less frequent with LOCM compared with HOCM and that iso-osmolar contrast media may be even less nephrotoxic than LOCM, it is reasonable to question what role osmolality per se may have in the pathogenesis of contrast-induced renal injury.

Additional putative evidence of nephrotoxicity from the increased viscosity of iso-osmolar contrast media is suggested by experiments using laser-Doppler flow measurements that have demonstrated that iodixanol resulted in a significantly greater decrease in medullary blood flow and oxygenation compared with both HOCM and LOCM.[7,24] Reduction in medullary blood flow was less marked when iodixanol was warmed from 20° to 37° C, reducing its viscosity.

In summary, experimental studies provide conflicting data regarding the role of osmolality in the pathopathy of contrast media nephropathy. The reports of reduced clinical CIN with iso-osmolar contrast media and experimental observations that these agents produce abnormalities

Table 1
Contrast-Induced Nephropathy: Prospective Randomized Trials of Low-Osmolar Contrast Media Versus High-Osmolar Contrast Media

			Incidence of CM-AN (n/N) (%)		Incidence of CM-AN Based on Risk Factors (n/N) (%)							
					-RI/-DM		-RI/+DM		+RI/-DM		+RI/+DM	
	LOCM/ HOCM Studied	Definition of CM-AN	LOCM	HOCM	LOCM	HOCM	LOCM	HOCM	LOCM	HOCM	LOCM	HOCM
Schwab et al.[56]	Iopamidol Diatrizoate	↑ Scr ≥0.5 mg/dL within 48 hr	24/23 (10.2)	17/208 (8.2)	NA	NA	NA	NA	NA*	NA*	NA*	NA*
Harris et al.	Iohexol Iothalamate	↑ Scr ≥25% within 48 hr	1/51 (2.0)	7/50 (14)	-	-	-	-	1/35 (2.9)	4/41 (9.8)	0/16 (0)	3/9 (33.3)
Taliercio et al.[55]	Iopamidol Diatrizoate	↑ Scr ≥0.5 mg/dL within 1 to 5 d	7/147 (4.8)	16/142 (11.3)	-	-	-	-	3/127 (2.3)	10/122 (8.2)	4/20 (20)	6/20 (30)
Rudnick et al.[54]	Iohexol Diatrizoate	↑ Scr ≥1.0 mg/dL within 48 to 72 hr	19/591 (3.2)	42/592 (7.1)	0/188 (0)	0/171 (0)	1/153 (0.7)	1/162 (0.6)	6/148 (4.1)	11/148 (7.4)	12/102 (11.8)	30/111 (27)
Barrett et al.[38]	Iohexol Iopamidol Iothalamate Diatrizoate	↑ Scr ≥25% by 48 hr	5/132 (3.8)	8/117 (6.8)	-	-	-	-	2/108 (1.9)	4/105 (3.8)	3/24 (12.5)	3/12 (25)
Moore et al.	Iohexol Diatrizoate	↑ Scr >0.4 mg/dL and >33% within 48 hr	13/479 (2.7)	13/450 (2.9)	9/382† (2.4)	6/380† (1.6)	NA	NA	4/96† (4.2)	7/64† (4.2)	NA	NA

*28 patients with RI.
†Totals include 119 DM patients, of whom 43 had RI and DM.
CM-AN, Contrast media-associated nephropathy; DM, diabetes mellitus; HOCM, high-osmolar contrast medium; NA, not available; LOCM, low-osmolar contrast medium; RI, pre-existing renal insufficiency; Scr, serum creatinine.

in renal blood flow and oxygenation suggest that some other chemical or physical property of contrast media besides hyperosmolality is responsible for some, if not all, of the nephrotoxic effects of contrast media. This conclusion does not exclude the possibility that hyperosmolality may still be a contributing factor in the pathogenesis of CIN. Historically, the results of most experimental studies of acute renal failure (including contrast nephropathy) do not correlate with clinical observations. Given the limitations and conflicting findings of the experimental studies cited in this review, one should not dismiss the initial clinical reports of diminished nephrotoxicity following administration of iso-osmolar contrast media.[15]

Clinical Studies of Low-Osmolar Contrast Media

LOCM have become widely accepted because of their reduced incidence of associated adverse effects compared with HOCM. Experimental observations in in vitro models and animals have demonstrated that LOCM are associated with smaller reductions in RBF and GFR and decreased albuminuria, enzymuria, and histologic damage compared with HOCM, which has led to speculation that LOCM may be associated with less clinical nephrotoxicity.[25]

Initial reports of the use of LOCM in diagnostic radiologic studies established that these agents were capable of causing a wide clinical spectrum of CIN. Despite these reports, it remained unclear if LOCM were associated with less risk of CIN than were HOCM. Initially, several prospective studies comparing the incidence of CIN between LOCM and HOCM were published (Table 1).[26–29] In these studies, either no differences in CIN were demonstrated between LOCM and HOCM, or, if

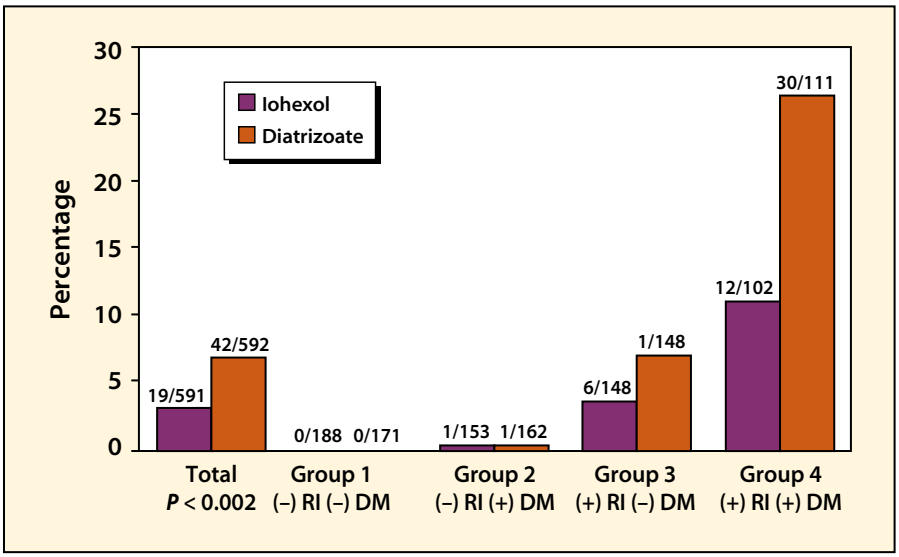

Figure 2. *Iohexol Cooperative Trial. Percentage of patients who developed contrast-induced nephropathy with diatrizoate and iohexol according to risk group. Reprinted with permission from Rudnick et al.*[30]

there were differences favoring LOCM, the differences were small and interpreted as clinically insignificant. However, these studies were limited by the small number of azotemic (high-risk) patients studied.

In an attempt to resolve this question, a large randomized, prospective, double-blind study was performed comparing the incidence of CIN in patients who received the LOCM iohexol or the HOCM diatrizoate.[30] In this study, 1196 patients were evaluated, of whom 509 were azotemic. This latter group contained 213 patients with both diabetes and azotemia. Similar to previous studies, the incidence of CIN was negligible in nonazotemic patients, regardless of whether diabetes was present or not (Figure 2). However, in azotemic patients without diabetes, the incidence of CIN was 7% and 4% in patients who received LOCM and HOCM, respectively. In the group with both azotemia and diabetes, the incidence of CIN was 27% in patients who received HOCM and 12% in those who received LOCM (Figure 2). The findings of this study were supported by a more recent meta-analysis of 25 trials, which demonstrated that the risk of CIN was 40% lower with LOCM than with HOCM.[31]

Conclusion

During the past 25 years, the osmolality of contrast media has progressively decreased with the introduction of LOCM and, more recently, iso-osmolar contrast media. With each reduction in osmolality, clinical studies have demonstrated a concomitant reduction in the incidence of CIN. Experimental studies, however, have been inconsistent in the demonstration that osmolality is an important pathogenetic mechanism or that reductions in osmolality are associated with less nephrotoxicity. Although it appears clear that LOCM are less nephrotoxic than HOCM in patients, additional large prospective, randomized clinical studies need to be conducted to definitively demonstrate that iso-osmolar contrast media are the least nephrotoxic in the clinical setting. ■

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Main Points

- Disturbances in renal hemodynamics and direct tubular epithelial cell toxicity are currently believed to be the primary mechanisms of contrast-induced nephropathy (CIN).
- Clinical trials have demonstrated that CIN in patients at high risk for this complication is less common with low-osmolar contrast media compared with high-osmolar contrast media.
- In the Iohexol Cooperative Trial, the incidence of CIN in patients with renal insufficiency without diabetes was: diatrizoate, 7%, and iohexol, 4%. In patients with renal insufficiency and diabetes, the CIN incidence was: diatrizoate, 27%, and iohexol, 12%.
- Recent trials suggest that iso-osmolar contrast media may be less nephrotoxic than low-osmolar contrast media.
- The pathogenetic role of hyperosmolality per se in the pathogenesis of contrast nephropathy is controversial.

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