Contrast Induced Nephropathy: Pathogenesis and Prevention

Internal Medicine Grand Rounds
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INTRODUCTION

Contrast induced nephropathy (CIN) has become a major clinical concern, particularly with imaging procedures moving to center stage in the diagnosis and treatment of disease in our aging population. Since 1987, the number of percutaneous coronary interventions (PCI) has increased by 326% [1]. It was estimated that in the year 2003, 80 million doses of contrast were given worldwide [2]. This expanded use is due in part to improvements in and expanded choices of diagnostic and therapeutic radiologic procedures for detecting and intervening in diseases, and in part to an increasingly heavy burden of cardiovascular disease, chronic kidney disease, and diabetes in an aging population. Most of the very diseases that we are attempting to diagnose and treat pose the greatest risk for development of CIN.

CIN is also of great interest to clinical and laboratory researchers as it is a form of acute renal failure where the time of injury is known with precision. This knowledge allows for the development of diagnostic tools, preventive measures, and therapeutic interventions that are not currently possible with most other forms of acute renal failure.

In this Grand Rounds, I will describe the natural history, incidence, risk factors, pathogenesis, contrast agents, and review of preventive measures that have been and are currently used to prevent its development. I will finish with an expert consensus panel recommendations about how to avoid radiocontrast nephropathy.

Case History

A 75 year old veteran with CAD and prior bypass surgery was admitted with unstable angina. Past Medical History: Type 2 Diabetes. Physical Exam: Hypertension. Labs: Serum Cr 3.4, hyperlipidemia. Hosp Course: Prior to cardiac catheterization, he received 0.45 % saline + 75 mEq $NaHCO_3$ at 75 ml/hr for 12 hours prior to and after catheterization. He also received 600 mg of oral N-acetylcysteine (N-Ac) twice daily the day before and after the first catheterization. At cath, the stenotic lesions could not be stented. Two days later, because of persistent chest pain and elevated ST segments, the patient returned to the cath lab. Neither N-acetylcysteine nor volume expansion were

reinstituted before the second catheterization. No acute thrombi were found. CIN developed the next day requiring four hemodialysis treatments.

BACKGROUND

One might ask why such a concern over a disease that occurs infrequently and when it does develop, a rapid recovery is the norm. CIN is not a benign disease, either in the short or long term [3-6]. In-hospital mortality rates for CIN are 22-35% in very large retrospective series with a marked increase in the risk of dying over the next five years [5, 6]. The odds of dying in-hospital following CIN are proportional to the elevation of serum creatinine from baseline [3]. Development of CIN also appears to increase the likelihood that a patient will develop chronic kidney disease in the months subsequent to contrast exposure [4].

DEFINITION OF CIN AND NATURAL HISTORY.

Most clinical trials for the past two decades have used either 1) an absolute rise of serum creatinine of 0.5 mg/dl or greater within 48 hours of exposure to contrast, or 2) a relative 25% increase in serum creatinine from baseline within 48 hours of exposure. Solomon and Barrett [7] emphasized that to compare similar degrees of renal injury, i.e. loss of glomerular filtration capacity, the relative change in serum creatinine is more informative than the absolute change. However, the use of a small and arbitrary absolute or relative change in serum creatinine as an outcome measure is insensitive. A stable and unchanged serum creatinine following administration of radiocontrast may miss what can be a significant fall in measures glomerular filtration rate [8]. In the future, serum creatinine may be replaced with more sensitive markers, or at least a meaningful rise serum creatinine may be redefined more stringently. The recent move to rename acute renal failure as "acute kidney injury" includes the proposal for a lower increase of 0.3 mg/dl in serum creatinine as evidence of acute kidney injury [9, 10]. While this lower threshold value has not been used in many studies of CIN, an absolute increase of as little as 0.25-0.5 mg/dl in serum creatinine within 3 days of coronary angiography was linked to a significant increase in 30 day in-hospital mortality [3]. Other surrogate markers of GFR such as cystatin C may prove more sensitive and useful than serum creatinine [11]. Lastly, NGAL (neutrophil gelatinase-associated lipocalin), an early predictive biomarkers of renal tubular injury was shown to have high sensitivity and specificity in identifying CIN in children who had undergone elective cardiac catheterization [12].

What would be desirable in studies of CIN and other investigations of acute renal failure is a "hard" rather than "soft outcome" [13]. Examples of these would be death, need for dialysis, and re-hospitalization. Fortunately for patients and unfortunately for investigators, these are very uncommon occurrences and would require very large numbers of patients before a significant number of events occurred. To accomplish this goal requires large multi-center trials.

The clinical course of CIN is characterized by a rise in serum creatinine within 24 hours of the contrast exposure that peaks within 3-7 days, and returns to baseline within 14

days. Most patients are not oliguric (i.e. <400 ml/day), although urine volume usually falls. Few patients require dialysis treatment, less than 1%, and it is required usually in those who are unstable in some other way, such as patient who develop CIN following PCI for acute myocardial infarction[5].

INCIDENCE

Nash et al (2002)[14], repeating a study originally published by the senior author in 1979 [15], found that contrast-induced nephropathy (CIN) was the 3rd leading cause of hospital acquired acute renal failure. The incidence of radiocontrast nephrotoxicity varied little over the 17 years, causing 12% of the cases of acute renal failure in 1979 and 11% of the cases in 2002. Cardiac catheterization and coronary angiography accounted for 49% of cases of acute renal failure. The risk of developing CIN after coronary angiography in a large cohort is 3-14% [5, 6]. However, for more elective procedures such as diagnostic computed tomography, the risk of developing CIN is very low, and likely due to the low dose of contrast, usually less than 100 ml.

RISK FACTORS

Many conditions and underlying disorders predispose to RCN (Table 1). Chronic kidney disease leads the list and is often the reason a diagnostic study is deferred or delayed, as the risk of CIN can be quite high [16]. Diabetes carries almost the same

Table 1
Risk Factors for CIN

Chronic Kidney Disease	Hypotension
Diabetes Mellitus	Multiple Myeloma
Congestive Heart Failure	Concomitant Medications
Myocardial Infarction	NSAIDs
Age	Diuretics
Renal Transplantation	Anemia
Hypovolemia	

risk for CIN as chronic kidney disease and is likely explained by the either overt or covert diabetic renal disease [17]. Patient with Class IV heart failure are also at particular risk, likely representing multiple factors including the presence within the kidney of the same disease(s) that caused the heart to fail e.g. atherosclerosis, combined with a reduced effective arterial blood volume and its effect to decrease GFR. Older patient are at more risk as they generally have more vascular disease, which is often the indication for the study. Volume depletion and hypotension are major risk factors, and avoidance of contrast in their presence, or correcting them before giving contrast is now central to preventive measures that will be described later. It is noteworthy that only a few decades ago it was standard procedure to prepare patients for contrast studies with an overnight fast from food and fluids so that the image would be enhanced. How many cases of

contrast nephropathy this now abandoned practice caused can only be guessed. New contrast agents and newer imaging devices, discussed later, have allowed improved image quality without the need for volume depleting measures. Why volume depletion enhances the likelihood of developing CIN is not precisely known, but increased renal vasoconstrictive influences, increased oxygen consumption from increased sodium reabsorption, and increased oxidative stress in renal tissue are likely factors [18]. Patients with multiple myeloma, particularly in the presence of heavy Bence Jones proteinuria, seem to be at particular risk from radiocontrast, although proper preparation of the patient beforehand may permit these studies in certain patients [19]. Drugs that affect extracellular volume such as diuretics, and NSAIDs that impair vasodilating renal prostaglandins should be avoided. Continued use of ACE inhibitors or ARBs in patients undergoing cardiac catheterization is not associated with an increased incidence of CIN [20]. Nikolsky et al [21] identified low hematocrit as a significant risk factor in 6,773 patients who underwent PCI. Whether correcting a low hematocrit prior to contrast exposure would lessen the risk for CIN remains unexamined. It is not clear if a renal transplant puts a patient at greater risk for CIN. A small, retrospective study reporting a 21% incidence of CIN is confounded by the high prevalence of diabetes, transplant rejection, potentially nephrotoxic anti-rejection drugs, and failure to volume expand pre-contrast in 50% [22].

Scoring tools are available to identify patients most at risk for CIN and death [23, 24]. Bartholomew et al [24] retrospectively examined a large data base of patients who had undergone PCI and divided the cohort into a derivation group (1993-1998) and a validation group (1999-2002). Multivariable analysis of the two data bases yielded seven strong independent variables (Table 2) that were used to establish a scoring system to predict the risk of CIN and death (Table 3). No patients with a risk scores <1 developed CIN; 26% of patients with a score ≥9 developed CIN.

Table 2. Risk Factors for CIN after PCI [24]

Risk Factor	**Odds Ratio**	**Score**
Creatinine clearance < 60 ml/min	5.0 (3.6-6.9)	2
Intra-aortic balloon pump	5.1 (3.6-7.2)	2
Urgent/emergent procedure	4.4 (2.9-6.4)	2
Diabetes Mellitus	3.1 (2.3-4.2)	1
Congestive heart failure	2.2 (1.6-2.9)	1
Hypertension	2.0 (1.4-2.8)	1
Peripheral Vascular Disease	1.9 (1.4-2.7)	1
Contrast Volume > 260 ml	1.8 (1.4-2.3)	1

The importance of this study is that it highlights and attempts to quantify risk factors beyond just the pre-study serum creatinine.

Table 3

CIN Risk Score In Validation Group [24]

Risk Score Group	n	Nephropathy (%)	Death (%)
0-4	6,582	0.2	0.2
5-6	1,520	2.8	2
7-8	389	10	9
9-11	36	28	17

PATHOGENESIS

Following radiocontrast administration, the renal vasculature in experimental animals responds in a biphasic manner with a brief initial vasodilatation followed by a more prolonged vasoconstriction. However, when renal blood flow was directly measured by thermodilution in humans with chronic kidney disease undergoing cardiac angiography, a biphasic response was not seen and most patients had an increase in renal blood flow (Figure 1) [25]. Moreover, in the six patients who developed CIN, only two had a transient decrease

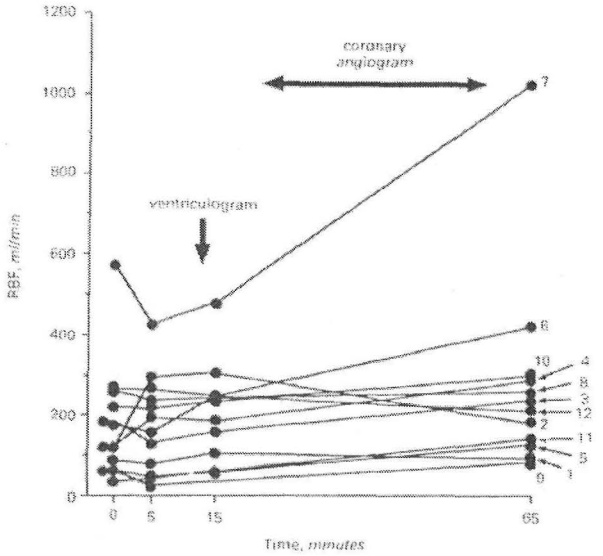
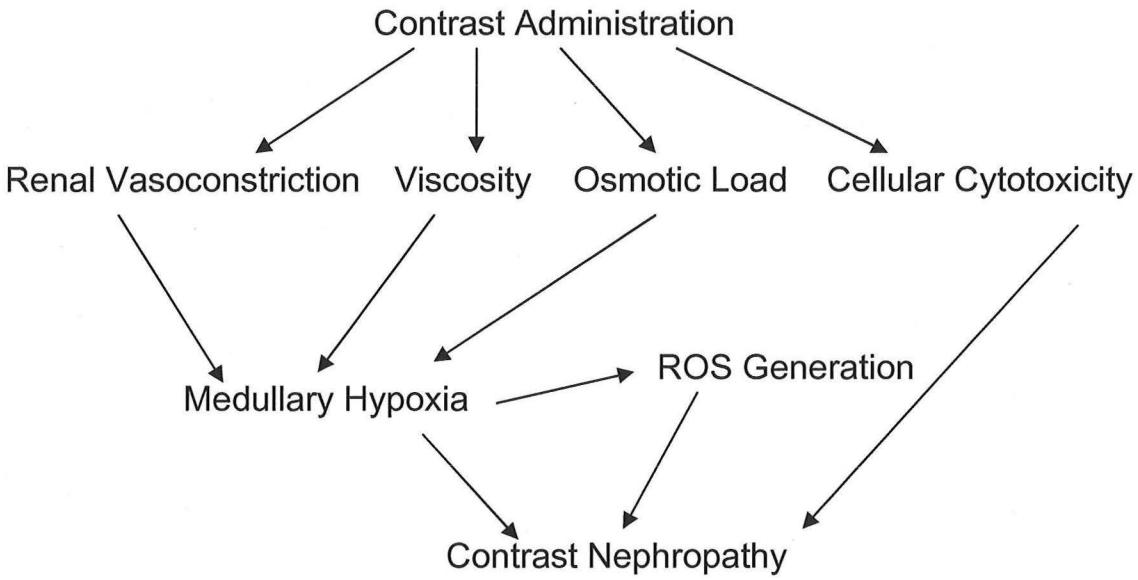


Figure 1. Thermodilution measurement of renal blood flow before and after administration of radiocontrast in patient with chronic kidney disease [25].

in renal blood flow. Thus, for renal vasoconstriction to be an important mechanism in the development of CIN, it is likely occurring at the local level, namely in the renal medulla.

Medullary Hypoxia. Figure 2 schematically summarizes the commonly accepted pathways thought to participate in CIN.

Figure 2



The central component of this model is medullary hypoxia. The most extensive work on the effect of radiocontrast on renal medullary hemodynamics comes from the studies of Brezis and colleagues [26-28]. A key observation is that in the normal state, renal outer medullary blood flow is low and the tissue is hypoxic compared with the renal cortex, due largely to the countercurrent exchange of oxygen in the vasa recta. A low medullary blood flow is a physiologic requirement to maintain the steep gradients for solute and water reabsorption by the distal nephron. At the same time, the outer medulla houses the thick ascending limb which performs the important, heavily oxygen dependent work of sodium reabsorption. Because of these competing requirements, i.e. low blood flow and oxygen dependent ion transport, this part of the kidney lives precariously close to a state of hypoxic cell injury. A number of redundant mechanisms that regulate blood flow and tubular transport cooperate to keep this system functioning (Table 4).

Table 4

Regulators of Medullary Blood Flow and Tubular Transport

Vasodilators	**Vasoconstrictors**	**Transport Inhibitors**
Nitric Oxide	Endothelin	Prostaglandin E2
Prostaglandin E2	Angiotensin II	Adenosine
Adenosine	Vasopressin	Dopamine
Dopamine		
Urodilatin		

Radiocontrast contrast administration can disrupt this fine balance. Radiocontrast sharply decreases outer medullary oxygen tension, at the same time that sodium delivery to the thick ascending limb is likely to be increasing due to an osmotic diuresis from the contrast agent [28]. However, this effect to reduce medullary oxygen tension can occur independently from the osmolality of the contrast agent. Liss et al showed that both low osmolar and iso-osmolar contrast reduce medullary PO_2 in the rat [29]. A later study showed that the effect of contrast to reduce medullary PO_2 could not be blocked with an adenosine A1 receptor antagonist [30]. This latter finding is not surprising, since adenosine has a complex effect on renal blood flow, being a vasoconstrictor in the renal cortex and a vasodilator in the renal medulla [31].

Medullary derived prostaglandins and nitric oxide protect against the renal vasoconstrictive influences of radiocontrast, Figure 3 [27]. In this study, inhibition of prostaglandins with

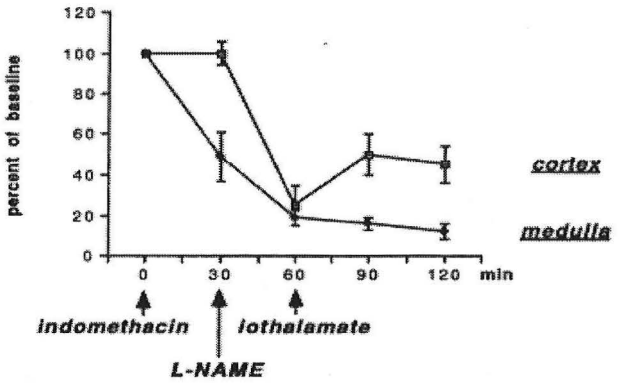


Figure 3. Sequential changes in cortical and outer medullary blood flow after sequential administration of indomethacin, L-NAME (an inhibitor of nitric oxide synthetase), and iothalamate [27].

indomethacin and inhibition of nitric oxide synthesis with L-NAME prior to exposing the rat kidney to radiocontrast caused a marked reduction in medullary blood flow to 12% of baseline values. At 24 hours post contrast, these animals had a 74% reduction in GFR with necrosis of 49% of medullary thick ascending limbs. This severe outcome was not seen when contrast was given in combination with either indomethacin alone or L-NAME alone. Endothelium-derived vasorelaxation is impaired in diabetes, chronic kidney disease, hypertension, and heart failure [32-35], diseases at high risk for CIN. Thus, these laboratory studies suggest a link that may provide a partial explanation for this increased risk.

Other important regulatory mechanisms involved in medullary blood flow and oxygen requiring tubular transport are adenosine as a locally produced medullary vasodilator and inhibitor of transport, and endothelin and angiotensin II, potent locally produced vasoconstrictors.

Reactive Oxygen Species. Chronic renal failure, diabetes, hypertension, and heart failure, all high risk disorders for developing CIN, are conditions where high oxidative stress is present [36-39]. A state of high oxidative stress is described as in imbalance favoring the generation of reactive oxygen species over the antioxidants that keep them in check. One of the effects of high oxidative stress in the renal medulla is a reduction in nitric oxide, an important regulator of medullary renal blood flow.

The rationale for using anti-oxidants like N-acetylcysteine to prevent clinical CIN, described later, derives in large part from the experimental work of Bakris and colleagues [40] who demonstrated in a canine model that the transient reduction in glomerular filtration rate following a radiocontrast infusion (the high osmolar agent sodium and meglumine diatrizoate) could be blocked by a continuous intravenous infusion of allopurinol which blocks xanthine oxidase an enzyme that generates free radicals, or by the continuous intrarenal infusion of superoxide dismutase, an enzyme which scavenges free radicals. The rise in renal venous blood malondialdehyde (MDA) concentration, a lipid peroxidation product that rose immediately after contrast administration in controls, was attenuated in the treated groups. Also, oxidative stress appears to be critically important in the pathogenesis of ischemia/reperfusion injury and acute allograft rejection, two other forms of acute kidney injury [41]. Experimental models of acute kidney injury suggest that therapeutic strategies that reduce the formation of ROS or promote activity of the NO system should reduce the incidence of ischemic renal injury, a likely pathway operative in CIN.

Direct Cytotoxicity. How much of CIN is due to the physiochemical properties of radiocontrast and how much is due to direct cytotoxicity is unclear. Radiocontrast agents, particularly hypertonic agents, are toxic to mesangial and tubular cells in vitro [42-44]. Mechanism invoked for this direct damage are cellular energy failure, disruption of calcium homeostasis, disturbed apoptosis, and oxidative stress [42, 44, 45]

RADIOCONTRAST AGENTS

Pharmacokinetics. The pharmacokinetics of radiocontrast agents are shown on Table 5.

Table 5
Pharmacokinetics of Radiocontrast

- Water Soluble
- Minimal Protein Binding
- Excretion by Glomerular Filtration
- No Metabolism
- Efficient Removal by Dialysis

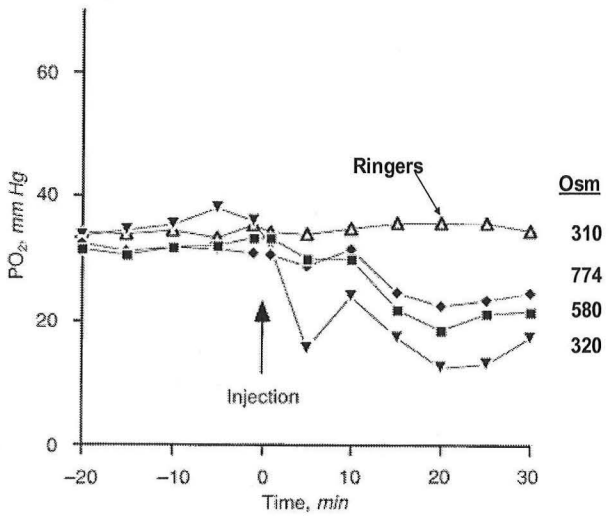
Table 6 details and compares the four types of radiocontrast agents based on molecular structure. While the agents are formulated in a variety of iodine concentrations, the agents chosen for this table have equal iodine concentration so as to easily compare osmolality, iodine ratio (a higher ratio give better x-ray attenuation), and viscosity. Radiocontrast agents have evolved from initially being ionic, high osmolality agents to the current agents which are low or iso-osmolar and generally are non-ionic, although some low osmolar agents are ionic. High osmolality agents are no longer in clinical use.

Radiocontrast agents are characterized by their low lipid solubility, low chemical activity, relatively small molecular weights, minimal protein binding, and rapid renal excretion with a T ½ of 1-2 hours. In experimental animals, small quantities of iso-osmolar radiocontrast can be detected in apical vacuoles of the proximal tubule with urinary excretion of trace amounts detectable 28 days later [46]. Non-ionic agents are more likely to be internalized in proximal tubules than are ionic. A similar observation is documented in human biopsy specimens following ionic high osmolality radiocontrast administration and has been termed "osmotic nephrosis," although no functional impairment has yet been associated with this finding (Moreau 1975).

Table 6 Radiocontrast Agents Compared

Agent	Iodine (mg/ml)	Osm mOsm/Kg H20	Iodine Ratio	Viscosity cps @ 37°	Type
Iothalamate	325	1695	3:2	2.8	Ionic monomer
Ioversol	320	700	3:1	6.0	Non-ionic monomer
Ioxaglate	320	580	3:1	7.5	Ionic dimer
Iodixanol	320	290	6:1	11.4	Non-ionic dimer

Viscosity. The trade-off for reducing the osmolality of radiocontrast is an increase in viscosity. To the end user, this becomes immediately apparent in the difficulty encountered when the contrast is pushed through a catheter. The role of high contrast viscosity in the causation of CIN is not clear. Iso-osmolar agents impair oxygen tension in the renal medulla as much, if not more than low osmolar agents Figure 4 [29].

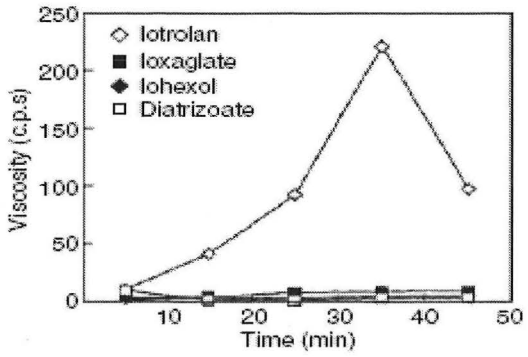


Liss, Kid Internat; 1998; 53: 698

Figure 4. Effect of two low osmolar and one iso-osmolar contrast agents on medullary PO_2 in the rat [29].

In a series of studied in the rat, Ueda et al showed that iso-osmolar iotrolan caused a sustained depression of single nephron glomerular filtration rate (SNGFR) [47], a marked and sustained increase in proximal and distal tubular hydrostatic pressures [48], and a dramatic rise in urine viscosity (Figure 5) [49]. It is postulated that as renal interstitial pressures may rise to values as high as 50 mm Hg the result may be medullary ischemia and a decreased GFR [50]. Whether these hemodynamic effects of iso-osmolar agents translate into risk factors for CIN in humans await further study.

Figure 5. Effects of iso-osmolar Iotrolan compared to low osmolar (ioxaglate, iohexol) and high osmolar (diatrizoate) contrast on pelvic urine viscosity in the rat.



Volume of Contrast. Higher volumes of administered contrast directly increases the likelihood of developing CIN [51]. McCullough et al [5] found that no patient undergoing coronary angiography developed CIN when the volume of contrast was less than 100 ml. Unfortunately, in the current era of aggressive therapeutic coronary intervention, the typical patient undergoing coronary angiography receives 250-300 ml of contrast and often much more per procedure [6]. The risk of CIN following CT procedures that employ fixed, standard volumes of intravenous contrast is quite low, even for patients at higher risk.

Type of Contrast. Low and iso-osmolar contrast agents have completely replaced high osmolar contrast agents. While high osmolar agents were quite safe in patients with normal renal function, the incidence of CIN in high risk patients was nearly two fold higher compared with low osmolar agents[52]. Allergic reactions and other unpleasant side effects of high osmolar agents also are significantly less with low osmolar agents.

However, it is not clear that the incidence of CIN with low osmolar agents is any different with iso-osmolar agents. The NEPHRIC Study [53] was a randomized controlled trial of iso-osmolar iodixanol versus low osmolar iohexol in high risk diabetics undergoing coronary and vascular angiography and reported significantly less CIN in patients exposed to iso-osmolar contrast. The study can be criticized because of the relatively small number of patient, 64 in each group, and thus was underpowered. McCullough et al performed a meta-analysis of 16 studies comparing the nephrotoxicity of low osmolar versus iso-isomolar contrast agents in [54]. They found that iso-osmolar agents were less nephrotoxic, especially in patient with diabetes. However, a recent study from Liss et al, 2006[4], indicates that there is an increase in long term kidney injury in patient who are exposed to iso-osmolar contrast media (i.e. iodixanol) compared with low osmolar contrast (ioxaglate), apart from whether the patient developed acute CIN. This study was extracted from the Swedish Coronary Angiography and Angioplasty Registry that includes 23 hospitals and analyzed data from 57,000 patients from 2000-2003. During this time, patients received either iodixanol (n=45,485) or ioxaglate (n=12,440). In subsequent months, clinically significant renal failure or the need for dialysis occurred more frequently in patients who received iso-osmolar contrast iodixanol than those who received ioxaglate. This association persisted in subgroup analysis for patients with underlying renal disease or diabetes. Hydration protocols and volume of contrast was similar in the iso-osmolar and low osmolar groups.

A preliminary report comparing a low osmolality agent (iopamidol) with an iso-osmolar agent (iodixanol) in a randomized, multicenter, double-blind trial of 153 high risk patient undergoing contrast enhanced multidetector CT failed to detect a difference in CIN between the groups [55].

Most of these large comparison trials are industry designed and sponsored making it difficult to draw conclusions that are totally free from bias. At present, there does not appear to be a clear advantage to the use of iso-osmolar agents over low osmolar agents.

PREVENTION

Sodium Chloride. Solomon et al [56] compared the effects of saline expansion plus either an osmotic diuretic, mannitol, or a loop diuretic, furosemide, compared to saline expansion alone on the development of contrast nephropathy in 78 high risk patients[56]. Neither diuretic afforded protection, and patients receiving furosemide had a significant increase in the incidence of acute renal failure. The saline protocol for all three groups was 0.45% saline for 12 hours before and 12 hours after contrast exposure. This study more than any was the impetus to make prior saline expansion a routine part of the pre-study preparation for high risk patients undergoing contrast exposure.

Mueller et al [57] Hypothesizing that isotonic saline would be more protective, randomized 685 patient to receive isotonic saline and 698 patient to receive 0.45% saline prior to coronary angioplasty. Baseline renal function was normal in most patients. CIN developed in 5 patients receiving isotonic saline (0.7%) compared with 14 patient (2.0%) receiving 0.45% saline, $p<0.04$. Three groups in particular appeared to benefit from isotonic saline: women, patients with diabetes, and those receiving 250 ml or more of contrast.

It is surprising that a study examining saline hydration alone was published only recently. Trevidi examined the incidence of CIN in 53 patient pre-hydrated with intravenous normal saline for twelve hours before and twelve hours after radiocontrast for coronary angiography[58]. The control group received oral hydration only. During the subsequent 48 hours, the control group had a ten fold higher incidence of CIN and the study was terminated early for safety concerns.

While the message seems clear that volume expansion with saline is a simple and beneficial preparation for high risk patients about to receive contrast media, it is not practiced uniformly. Weisbord et al [59] retrospectively examined the precontrast hydration patterns of a cohort of high risk patients who had no apparent preconditions that would make them ineligible for saline expansion. Sixteen percent of all eligible patients received no intravenous volume expansion. When intravenous volume expansion was used, it varied widely in total quantity, by procedure, and by treating specialty. Cardiology was the treating specialty most likely to adhere to the commonly accepted strategies for intravenous volume expansion. Internal medicine was the least likely to follow the strategies.

Sodium Bicarbonate. The ability of intravenous sodium bicarbonate to both volume expand, alkalinize the urine, and possibly reduce the generation of free radicals lead Merten et al [60] to use it to prevent CIN in a single center study of 119 patient undergoing a variety of intravenous contrasted studies. Patients were randomized to either isotonic saline or isotonic sodium bicarbonate beginning with a 3 ml/kg bolus followed by 1 ml/kg/hour for 6 hours post procedure. The results clearly favored sodium bicarbonate with only 1 of 60 patients (1.7%) developing CIN compared to 8 of 59 (13%) of the patients pretreated with normal saline. The study was stopped by the safety monitor before full enrollment because of the clear trend favoring the sodium bicarbonate group. However, this action has since been criticized as too aggressive, particularly since there were no predetermined criteria for terminating the study. On the otherhand, a preliminary report from Mayo Clinic retrospectively examining the role of sodium bicarbonate and N-acetylcysteine as preventive measures for CIN indicated an increased risk for CIN in patient treated with sodium bicarbonate compared to no treatment (OR=1.78)[61]. This association held after adjustments for covariates.

N-Acetylcysteine. N-acetylcysteine has been in clinical use to prevent CIN since 2000, following the report of Tepel et al [62] showing a 2% incidence of CIN in treated patients versus a 12% in controls. The study was prospective, randomized, and placebo controlled in high risk patients with chronic kidney disease. The proposed mechanism of protection by N-acetylcysteine was through its known antioxidant properties.

Several clinical studies have examined whether markers of oxidative stress can be detected after radiocontrast administration, but the results are inconclusive [63-65]. While N-acetylcysteine prevented a fall in urinary nitric oxide levels following radiocontrast administration, it had no effect on the urinary excretion of F2-isoprostanes, a marker of oxidative stress formed by the reaction of the superoxide radical with arachidonic acid [63]. Mild CIN developed in this study as glomerular filtration rate rose significantly at 24 hours in the N-acetylcysteine group, while falling significantly in the control group. However, another report showed a significant immediate increase in urinary F2-isoprostane levels post radiocontrast that was prevented with prior treatment with the antioxidant acetylcysteine, but there was no evidence that any patient developed CIN [65].

A puzzling aspect of most clinical trials with N-acetylcysteine [65-68], is the observation that serum creatinine in the N-acetylcysteine group not only did not rise after contrast, but actually fell significantly, raising the possibility that N-acetylcysteine might be influencing serum creatinine or glomerular filtration directly. Drager et al [65] noted that a significant increase in creatinine clearance persisted 48 hours after contrast exposure for coronary angiography in patients treated for 4 days with N-acetylcysteine that began two days before the procedure. Based on these clinical observations, Hoffman et al [69] investigated the effect of N-acetylcysteine on serum creatinine and creatinine clearance in 50 normal volunteers not exposed to radiocontrast. Four hours after N-acetylcysteine administration, serum creatinine fell significantly (0.85 ± 0.14 mg/dl to 0.82 ± 0.13 mg/dl, $P>0.05$). This change in serum creatinine was not accompanied by a change in another independent surrogate marker of glomerular filtration rate, Cystatin C ($0.75 \pm$

0.10 mg/dl to 0.74 ± 0.09 mg/dl, NS). A trend for a reduced serum creatinine persisted 48 hours post N-acetylcysteine in these normal subjects, but was no longer statistically significant. The authors ruled out an effect of N-acetylcysteine on the creatinine assay, as the results were the same by two different methods. They speculated that N-acetylcysteine had an effect on renal tubular creatinine secretion or muscle metabolism and interpreted their findings as casting doubt on the practice of administering N-acetylcysteine to protect against CIN.

After six years of use, the benefits of N-acetylcysteine in preventing CIN are still in doubt. Bagshaw [70], in a review of the data on N-acetylcysteine use to prevent CIN, noted that as of the time of that report, 19 randomized trials, 4 prospective non-randomized studies, and 11 meta-analyses have investigated whether N-acetylcysteine protects against CIN without producing a conclusive answer. Seven meta-analyses concluded that N-acetylcysteine was beneficial; 4 reported that the data was inconclusive [71]. The major issue cited for the discordant results of the meta-analyses was heterogeneity in the studies (e.g. variations in patient populations, co-interventions, eligibility criteria, primary outcomes).

A recent single center trial in patients with an acute myocardial infarction undergoing primary angioplasty by Marenzi et al [67] suggests that prior studies may have been inconclusive because the dose of NAC chosen was too low. They compared high dose N-acetylcysteine (1200 mg iv prior and two doses the following day) with a standard dose (600 mg iv prior and two doses the following day). The control group received placebo. All three groups received normal saline for 12 hours post procedure. The results showed a dose dependent protective effect for N-acetylcysteine against CIN. The rate for the composite end point of in-hospital mortality, CIN requiring renal replacement therapy, and the need for mechanical ventilation was 5%, 7%, and 18% in the high, standard, and placebo groups, respectively. Interpretation of these findings is confounded by the absence of pre-contrast saline expansion, a measure of proven benefit in preventing CIN that has become virtually a baseline precondition in studies examining pharmacologic interventions in CIN. These interesting findings will have to be confirmed in a larger group of patients.

In summary, NAC does appear to increase GFR in normals and increase or maintain GFR in some patients exposed to radiocontrast. Whether the latter effect is a direct protective effect on the kidneys, or an effect on creatinine transport or metabolism, or possibly an effect on cardiac function, as has been suggested, is unclear.

Other Pharmacologic Protective Strategies and Summary. Table 7 summarizes the findings and conclusions of the CIN Consensus Working Panel on pharmacologic strategies in the prevention of CIN [72]. The studies showing a positive result are generally single center, small studies with a statistically positive effect. Without larger, confirmatory studies, these findings cannot be accepted as definitive. The agents listed under neutral studies, although tested based upon sound animal studies or pilot studies in humans, have not consistently proven to be beneficial. Despite the conflicting evidence for the efficacy of N-acetylcysteine, it is likely to continue to have limited use pending a

definitive multicenter, randomized clinical trial. Negative results agents are viewed as having no benefit, potentially harmful, or their use is not recommended.

Table 7
Pharmacologic Agents for CIN Risk Reduction

Positive Results (potentially beneficial)

- Theophylline/aminophylline [73-75]
- Statins [76, 77]
- Ascorbic acid [78]
- Prostaglandins E_1 [79-81]

Neutral Results (no consistent effect)

- N-acetylcysteine (see discussion and references above)
- Fenoldopam [82, 83]
- Dopamine [84-87]
- Calcium channel blockers [88-90]
    - Amlodipine
    - Felodipine
    - Nifedipine
    - Nitrendipine
- Atrial natriuretic peptide [86, 91]
- L-Arginine [92]

Negative Results (potentially detrimental)

- Furosemide [56, 93]
- Mannitol [56, 86, 94]
- Endothelin receptor antagonist [95]

Adapted from ref [72]

Removal of Contrast Media by Extracorporeal Therapies. Radiocontrast is quickly and almost exclusively removed from the body by renal excretion. The kidney handles radiocontrast the same way that it handles inulin. It follows then that radiocontrast would be efficiently removed by variety of extracorporeal techniques [96]. Since the time of onset of CIN is known and the offending agent is easy to remove by dialysis, the logic for instituting dialysis during or immediately post procedure is reasonable. However, small studies have failed to show a significant beneficial effect of hemodialysis, when the procedure was performed immediately after contrast exposure [67, 97-99] or performed during the procedure [100]. One study suggested a possible harmful effect on renal function [99]. Continuous renal replacement therapies (CRRT), hemodiafiltration (CVVHD) and hemofiltration (CVVH), also have been studied [101-103]. When CVVHD was initiated immediately before and continued throughout the contrast study, no effect on the incidence of CIN was observed [101]. In the first of two CVVH study

by Marenzi et al [102], prophylactic hemofiltration was begun 6 hours before contrast administration in a high risk group (SCr = 3.0 mg/dl), held during the angiography procedure, resumed following the procedure, and continued for 18-24 hours [102]. The incidence of CIN in the treatment group, as measured by a 25% rise in serum creatinine from baseline, was 5% compared with 50% in the control group. This study has been criticized since CVVH while removing the radiocontrast also removed creatinine, and likely altered the outcome measure, and thus underestimated the incidence of CIN. A similarly designed study by the same author in an even higher risk group (SCr = 3.6 mg/dl), showed essentially the same degree of protection from CIN in the CVVH pre/post group, 3%, compared to 40% in controls [103]. The study also had a third experimental group receiving post contrast CVVH; no protection from CIN was noted in this group. The striking protection from CIN by pre/post CVVH in these two studies is impressive. However, the findings will require verification using a method of measuring GFR that is not influenced by the CVVH procedure itself.

A meta-analysis of these extracorporeal therapies published this year concluded that peri-procedural extracorporeal blood purification does not decrease the incidence of CIN [104]. In the case of CVVH, these patients require ICU monitoring and it is unlikely that it will ever prove to be a cost effective therapy, even if its efficacy can be proven in a large trial [105].

For patients receiving regular hemodialysis treatments that undergo radiocontrast studies, there is no evidence that immediate post procedure dialysis to remove the contrast load is warranted or even beneficial [106, 107] [108].

Gadolinium as an Alternative to Iodinated Contrast. Gadolinium has generally been thought of as a safe alternative contrast agent for patient with renal disease. Gadolinium based contrast agents are non-iodinated compounds given intravenously primarily during vascular imaging with MRA. In an off label use, they are also given intra-arterial for digital subtraction angiography (DSA). In low doses, i.e. 0.2-0.3 mmol/kg, gadolinium compounds are generally free of renal toxicity. Higher doses, i.e. >0.4 mmol/kg, particularly in high risk patients and when given intra-arterial, can produced CIN [109]. Early reports that these agents were less nephrotoxic than iodinated compounds and might be alternatives to iodinated contrast in patients at high risk were likely not comparing equal X-ray attenuating doses of the compounds [110]. The European Society of Urogenital Radiology has recommended against using gadolinium in high risk patients as these agents are likely to be more nephrotoxic than iodinated agents at equal attenuating doses [111]. Also, the cost of gadolinium contrast is 5 fold higher than iodinated contrast.

A new concern about the safety of gadolinium in high risk patients has arisen in the past few years that may be far more significant than possible nephrotoxicity. On Dec 22, 2006, the FDA sent a notice to radiologist, nephrologists, dermatologists and other healthcare professionals alerting them about the growing number of reports (90 to date) of the association between gadolinium exposure during MRI or MRA procedures in patient with advanced renal disease or ESRD and the development of nephrogenic

systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD) [112]. NSF/NFD is a disease primarily, but not exclusively, of the skin apparently restricted to patients with advanced kidney disease that has features of systemic sclerosis and myxedema. In patient with advanced renal disease or ESRD, changes in skin texture have occurred 2 days-18 mos after exposure to gadolinium, particularly in patients who were acidotic [113]. Gadolinium deposition has been demonstrated in dermal vessels [114]. The disorder may also involve the heart, liver, and skeletal muscle. While a causal link between gadolinium and NSF/NFD has not been conclusively established, the FDA recommends that gadolinium be used only if clearly necessary in patients with advanced kidney failure (GFR< 15 ml/min). An informative registry for reporting new cases and related information is available on line [115].

CONSENSUS PANEL RECOMMENDATIONS: 2006

Until evidence based recommendations are available, the following consensus recommendations of the recent international meeting of experts can be used as appropriate guides [116]. The risk for CIN should be evaluated in all patients, including the presence of underlying comorbidities such as chronic kidney disease, hypertension, heart failure, diabetes, dyslipidemia, myeloma, and nephrotoxic drugs. A serum creatinine is usually necessary in patient with these risk factors prior to receiving contrast. All patients should be encouraged to drink water liberally before the procedure. In patient, high risk patients should receive i.v. volume expansion. The type, total volume, and speed of administration must be guided by the urgency of the procedure and the clinical situation of the patient. Particularly in patient undergoing emergency coronary intervention, precipitation of congestive heart failure with rapid volume expansion must be weighed against the risk of developing CIN. I.v. fluids should be continued for at least 6 h after contrast exposure. The use of N-acetylcysteine can be considered in high-risk patients only, realizing that the evidence supporting its efficacy is equivocal at best. Low osmolality contrast media should be used for all patients; this recommendation includes iso-osmolar agent. The volume of contrast should be the minimum required for diagnosis and intervention. A reminder program that pointed out high contrast volume cases (> 300 ml) to interventional cardiologists and cardiology fellows significantly lowered the number of cases that exceeded this target [117]. NSAIDs, because of their ability to inhibit production of vasodilatory renal prostaglandins, should be discontinued several days prior to the procedure, if possible. Dipyridamole, a nucleoside uptake blocker that enhances the renal hemodynamic effects of radiocontrast, should be avoided on theoretical grounds [118, 119]. However, there are no clinical studies to support this recommendation. Lastly, for high risk patients, a serum creatinine should be obtained between 24-72 hours to document whether CIN has developed.

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