Dye-Induced Nephropathy

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The expanding use of imaging and interventional studies with iodinated radiologic contrast agents underscores the potential risk for dye nephropathy. Currently, dye-induced nephropathy is one of the leading causes of iatrogenic acute kidney failure, accounting for about 10% of renal failure in intensive care units. In this review, the pathophysiology of radiocontrast nephropathy is discussed, with a special emphasis on the importance of medullary hypoxic damage. The risk factors and clinical course of dye nephropathy, as well as its prevention or potential therapeutic interventions, are discussed in this perspective.

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The expanding use of imaging and interventional procedures with iodinated radiologic contrast agents underscores the potential risk for dye (radiocontrast) nephropathy. In the late 1960s, this iatrogenic disease entity was considered rare and exotic. Its incidence, however, quickly surged to involve some 40% of patients undergoing dye studies in the early 1980s, rapidly leading to the recognition of high-risk groups, such as diabetic patients and individuals with preexisting renal failure, low cardiac output, or dehydration. Subsequently, the incidence of dye nephropathy gradually declined to less than 3% of contrast studies, predominantly because of patient selection, because of the recognition of the importance of hydration status, and because of the introduction of the less-nephrotoxic low osmolar and nonionic agents. Nevertheless, dye-induced nephropathy remains one of the leading causes of iatrogenic acute kidney failure, accounting for about 10% of cases of acute renal failure in intensive care units. Among high-risk patients its incidence exceeds 20%, despite adherence to well-accepted protective measures, providing a formidable challenge to further improve preventive strategies.

Dye nephropathy is defined as a decline in glomerular filtration rate (GFR) after the intravascular administration of iodinated contrast agents. Kidney dysfunction is manifested with an increasing plasma creatinine level that peaks at 2 to 5 days, and usually returns to baseline values by 5 to 10 days. Dye-associated renal failure usually is nonoliguric and renal sediment is unremarkable in most cases. Fractional sodium excretion is often low, suggesting prerenal failure. Contrast nephropathy usually is self-limited, but some patients may run a protracted course and require renal replacement therapy, associated with increased morbidity and mortality, and prolonged hospitalization. The clinical diagnosis usually is evident under most circumstances, but other potential causes of acute renal dysfunction should be considered including nephrotoxic injury produced by other agents, sepsis, rhabdomyolysis, cholesterol emboli after arterial studies, shock, and other ischemic insults.

This review focuses on the pathophysiology of radiocontrast nephropathy, with a special emphasis on tubular hypoxic damage. In this perspective we analyze the mechanisms by which recognized risk factors might predispose to renal dysfunction after contrast studies, and critically evaluate the preventive/therapeutic strategies currently applied or investigated.

PATHOPHYSIOLOGIC BACKGROUND

Although recognized for some 40 years, the pathophysiology of contrast nephropathy remains a controversial issue. It is classified as acute tubular necrosis or toxic nephropathy but, in fact, very little is known about its true renal morphology in humans. Proximal tubular vacuolization has been encountered in renal biopsy examinations, but this change does not correlate with renal failure. Indeed, this alteration is present after dye administration under experimental settings, irrespective of kidney function. Urinary markers of tubular injury appear inconsistently, or are absent in humans with contrast nephropathy.

Many toxic nephropathies are believed to be mediated primarily through well-characterized direct tubular-cell toxicity, such as heavy metals, cisplatin, or aminoglycosides in experimental and

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clinical settings. Renal handling of the nephrotoxin predominantly determines the distribution pattern of tubular damage. The injury is dose dependent, and the contribution of perturbations is relatively marginal, with the exception of the hydration state. On the other hand, data regarding direct tubular toxicity of radiologic dyes is characterized poorly, and is occasionally (but not necessarily) attributed to hypertonicity. Contrast agents, once filtered through the glomerulus, are not reabsorbed or metabolized by tubular cells. Furthermore, although the dose of radiocontrast has been recognized as an independent risk factor for renal dysfunction, dye nephropathy rarely is encountered in the absence of predisposing factors. Whereas the incidence of dye nephropathy in the aged population (a predisposing factor by itself) was only 1.3%, in the absence of other risk factors it exceeded 60% in the presence of 3 or more confounding conditions. The latter effect is mediated by the control of GFR and proximal tubular reabsorption (both governing solute delivery to the distal nephron) and by the regulation of distal tubular reabsorption. Locally produced prostaglandins and nitric oxide, and the generation of adenosine from the breakdown of adenosine triphosphate, are major participants in these mechanisms. The location of mediator production and the distribution and density of its receptors are important in maintaining medullary oxygenation. For instance, adenosine, released during adenosine triphosphate consumption, exerts cortical vasoconstriction and inhibits transport activity in mTALs through A1 receptors, and induces medullary vasodilation through A2 receptors. Comparably, endothelin-1 exerts cortical vasoconstriction through ET-A receptors, but enhances medullary blood flow activating ET-B receptors. In this perspective, corticomedullary redistribution of blood flow and the activation of the tubuloglomerular feedback mechanism may be regarded as measures that maintain medullary oxygenation and prevent tubular hypoxic damage (see reference 3 for a detailed bibliography).

RENAL MEDULLARY OXYGENATION

Renal parenchymal oxygen supply is not homogenous: although the renal cortex is well oxygenated, a sharp decline in tissue \( \text{PO}_2 \) is noted at the corticomedullary junction, reaching 20 to 30 mm Hg under normal physiologic conditions. Medullary hypoxia is the price paid for the renal diluting/concentrating capacity, attributed to the unique architecture of the countercurrent system. Some 10% only of renal blood flow and oxygen supply are directed to the renal medulla through vascular bundles (vasa recta), originating from efferent arterioles of juxta medullary nephrons. Oxygen countercurrent diffusion from descending to ascending vasa recta further compromises medullary oxygen supply to some 8 mL/min/100 g tissue. This limited oxygen delivery is marginally sufficient for the metabolic needs for tubular transport, predominantly performed by medullary thick ascending limbs (mTALs) and S3 (straight) segments of the proximal tubule. Consequently, oxygen extraction by the renal medulla is near-maximal, reaching 79% of the regional oxygen supply, with only a small oxygen reserve left. This critical medullary oxygen balance is manifested by high levels of cytochrome AA3 in its redox state, and of unsaturated hemoglobin, detected by blood oxygen level dependent (BOLD) magnetic resonance imaging in humans.

Efficient mechanisms closely match medullary oxygen supply and demand by the determination of regional blood flow and metabolic activity. The latter effect is mediated by the control of GFR and proximal tubular reabsorption (both governing solute delivery to the distal nephron) and by the regulation of distal tubular reabsorption. Locally produced prostaglandins and nitric oxide, and the generation of adenosine from the breakdown of adenosine triphosphate, are major participants in these mechanisms. The location of mediator production and the distribution and density of its receptors are important in maintaining medullary oxygenation. For instance, adenosine, released during adenosine triphosphate consumption, exerts cortical vasoconstriction and inhibits transport activity in mTALs through A1 receptors, and induces medullary vasodilation through A2 receptors. Comparably, endothelin-1 exerts cortical vasoconstriction through ET-A receptors, but enhances medullary blood flow activating ET-B receptors. In this perspective, corticomedullary redistribution of blood flow and the activation of the tubuloglomerular feedback mechanism may be regarded as measures that maintain medullary oxygenation and prevent tubular hypoxic damage (see reference 3 for a detailed bibliography).

RADIOCONTRAST AND MEDULLARY OXYGENATION

The administration of a radiocontrast agent results in a marked decline of outer-medullary oxygenation. Using oxygen microelectrodes, we and others found that renal parenchymal \( \text{PO}_2 \) decreases, both in the cortex and in the medulla. This effect is most pronounced and dramatic in the outer medulla, where low ambient \( \text{PO}_2 \) declines further to values as low as 8 mm Hg after the injection of ionic high osmolar dye, and decreases by 50% with nonionic low osmolar agents. This dye-induced decline in medullary oxygenation can be restored by the inhibition of mTAL reabsorptive activity with the loop diuretic furosemide (see reference 3 for a detailed bibliography).

Hypoxia-induced factor 1 recently has been detected within the medulla and medullary rays
shortly after the administration of contrast (C. Rosenberger, unpublished data). This constitutively formed heterodimer rapidly accumulates during hypoxia because of the inhibition of the α subunit breakdown by oxygen-dependent prolyl hydroxylases. Thus, detection of hypoxia-induced factor, which initiates the cellular response to hypoxic stress, serves as an early indicator of dye-induced medullary hypoxia.

Radiocontrast-associated medullary hypoxia is mediated through several mechanisms: extrarenal effects consist of decreased cardiac output that may compromise renal blood flow; pulmonary shunts that lead to arterial hemoglobin desaturation; and a leftward shift of the oxygen-hemoglobin dissociation curve, decreasing oxygen availability to tissues. Blood fluidity may be altered as well. Renal effects can be divided into those compromising the renal microcirculation and those mechanisms that increase oxygen demand for tubular reabsorptive work.

Reabsorptive workload is enhanced by the solute load, and with the early, although transient, increase of GFR. Solute delivery to the distal nephron increases markedly, leading to enhanced distal tubular transport.

Altered microcirculation is attributed to abrupt changes in various mediators of the renal vascular tone. Dye administration increases plasma atrial natriuretic peptide (ANP), endothelin-1, vasopressin, renal adenosine, and prostaglandin E2. Sympathetic activity probably is enhanced as well. Renal effects can be divided into those compromising the renal microcirculation and those mechanisms that increase oxygen demand for tubular reabsorptive work.

RISK FACTORS FOR DYE NEPHROPATHY PREDISPOSE TO MEDULLARY HYPOXIA

Most risk factors for contrast nephropathy are characterized by structural or functional changes that can predispose to aggravation of hypoxic stress during dye administration. Enhanced systemic vasoconstrictive stimuli (angiotensin II, vasopressin, catecholamines) accompany effective volume depletion, for instance, in patients with heart failure, nephrosis, hypovolemic shock, or dehydration. The medullary microcirculation is deformed in pre-existing renal parenchymal disease (the result of structural parenchymal changes), and local oxygen insufficiency may be enhanced by increased reabsorptive workload in hypertrophic remnant nephrons. Enhanced tubular reabsorption and oxygen consumption may accompany early or uncontrolled diabetes owing to increased GFR and osmotic diuresis, respectively. Diabetes also is associated with defective nitrovasodilation, as is aging, hypertension, atherosclerosis, or hypercholesterolemia. Defective prostaglandin synthesis is encountered in aging and in patients receiving nonsteroidal anti-inflammatory agents. Additional exposure to other nephrotoxins and other comorbid states may intensify medullary hypoxic damage. Finally, the more nephrotoxic ionic and high osmolar radiocontrast agents exert more profound renal microcirculatory alterations in a dose-dependent fashion.
Thus, dysregulation of medullary oxygen balance is encountered in most circumstances considered to predispose to dye nephropathy.

ANIMAL MODELS OF CONTRAST NEPHROPATHY

With the limited knowledge of the human pathology of contrast nephropathy, appropriate animal models are essential for the understanding of its pathophysiology. In animals given radiocontrast dyes, proximal tubular vacuolization is a consistent finding, even when kidney function is well preserved (Fig 1). Electron microscopy reveals that these vacuoles represent membrane outpouching from infoldings of the basolateral membranes with other cellular elements being intact. Taken together with the irregular occurrence or absence of urinary markers of proximal tubular damage, such as kidney injury molecule-1 (KIM-1), proximal tubular vacuolization should be regarded as a marker for dye exposure, rather than an indicator of contrast nephropathy.

Similar to humans, healthy animals do not develop renal dysfunction when exposed to dye alone. Consequently, we developed experimental models of contrast nephropathy in rats using both dye administration and additional perturbations that mimic known clinical risk factors. Situations that were found to predispose to experimental dye-induced renal dysfunction include chronic salt depletion, angiotensin II infusion, prior uninephrectomy with compensatory hypertrophy of the remnant kidney, acute inhibition of prostaglandin or nitric oxide synthesis, enhancement of GFR by amino-acid infusion, and urine outflow obstruction. These insults, applied alone or in different combinations, were found to contribute to renal dysfunction independently, with the magnitude of renal failure (increasing plasma creatinine and urea levels, and declining creatinine clearance and tubular sodium reabsorption) proportional to the number of applied confounding factors. In all these protocols, renal morphology revealed variable medullary tubular necrosis that appeared as early as 15 minutes after the administration of the radiocontrast (Figs 2 and 3), predominantly affecting mTALs and, to a much lesser extent, S3 segments in the outer medulla and medullary rays. These morphologic changes range from reversible injury (mitochondrial swelling with maintained cellular integrity) to a more severe damage pattern (nuclear pyknosis and disruption of cell membranes). A gradient of damage was noted, maximal among mTALs at the midinterbundle zone, most remote from vasa recta. By 24 hours, tubular necrosis was maximal (Fig 4), affecting up to 80% of mTALs in the most severe models, occasionally associated with injured collecting ducts and damaged inner-medullary structures. Apoptotic cell death also was noted with a pattern of distribution comparable with that of tubular necrosis.

An additional morphologic hallmark of dye administration was outer-medullary vascular conges-
tion that appeared as early as 10 minutes after the administration of contrast, representing altered microcirculation. Tubular necrosis correlated with the extent of medullary congestion/stasis. It is conceivable that hypoxic endothelial dysfunction further perpetuated medullary hypoxic stress and renal dysfunction.

Taken together, these findings in animal models indicated that dye-induced altered medullary oxygenation may evolve into apoptotic or necrotic tubular injury when mechanisms designed to maintain medullary oxygenation are hampered. In different laboratories, other experimental models of dye nephropathy have been developed, superimposed on predisposing factors, such as hypercholesterolemia, diabetes or short periods of renal arterial clamping in rats, salt depletion and indomethacin in rabbits, and salt depletion or congestive heart failure in dogs. Detailed outer-medullary morphology was not available in most of these studies, but the experimental situations suggest an important adverse interaction between radiocontrast agents and medullary oxygen insufficiency.

OTHER POTENTIAL MECHANISMS OF RENAL DYSFUNCTION IN DYE NEPHROPATHY

Possibly, synergism exists between hypoxic, hemodynamic, toxic, and obstructive components in contrast nephropathy. The close functional-structural correlation, found in the more severe models of combined insults, is less evident in partial protocols with sparse focal damage. Indeed, renal dysfunction with minimal or absent tubular damage noted in these animals implies that reversible cell injury has been restored, or that renal microvascular response predominates. Such a hemodynamic reaction, probably mediated by tubuloglomerular feedback, helps in restoring medullary oxygenation by decreasing reabsorptive workload. Yet, it is manifested as diminished GFR with a low fractional sodium excretion. Additional confounding factors may include tubular obstruction by tubular cell casts, by oxalate and uric acid crystals, and by radiocontrast-precipitated Tamm Horsfall or Bence Jones proteins in patients with myeloma. Direct tubular cell toxicity also may coexist, as suggested predominantly by in vitro experiments involving free radical formation and lipid peroxidation. Tubular obstruction and reduced GFR caused by volume depletion may increase the transit time of the radiocontrast within the tubular lumen, and may intensify direct cellular toxicity. Finally, as stated earlier, contrast studies often are performed in critically ill patients treated with other nephrotoxins or displaying comorbid states such as sepsis or myoglobinuria that may exert additional tubulotoxic and hypoxic insults.
THERAPEUTIC IMPLICATIONS

Contrast nephropathy can be predicted to a large extent in high-risk patients, who often require image analysis. Being an expected sequela of an elective medical intervention, dye nephropathy has been a target for numerous trials of therapeutic or preventive measures. Most important are careful identification of patients at risk, avoidance of unnecessary contrast imaging in this population, and removal of coexisting perturbations, such as non-steroidal anti-inflammatory drugs and other nephrotoxins. So far, the only additional proven active interventions among high-risk patients include vigorous hydration and the use of low-osmolar and nonionic agents with the most minimal dose possible. Proper hydration decreases vasoconstrictive stimuli in volume-depleted individuals, may enhance dye elimination, and could increase GFR through natriuretic mediators. Intravenous administration of 0.45% saline at a rate of 1 mL/kg/h for 12 to 24 hours currently is recommended, starting 6 to 12 hours before the contrast study and extending up to 12 hours afterward. Hydration strategies with shorter periods of fluid administration and

Fig 3. Higher magnification of 1 μm plastic sections from animals cited in Fig 2. (A) A fragmented necrotic cell (arrow) with swollen mitochondria can be seen adjacent to the condensed dark cells of a MTAL. (B) Electron microscopy shows the marked differences between the MTAL condensed cellular elements (upper left) and unremarkable collecting duct (lower right). (C) Necrotic cell death with the associated mitochondrial swelling (arrows) is quite different than the condensed adjacent cell. Magnification: 1 μm plastic section ×700; electron microscopy ×760; × 1,800.
partial substitution of the preceding regimen with oral hydration are suggested. The use of 0.9% saline may be superior among high-risk patients. The substitution of high osmolar ionic agents with the newer generation of low osmolar and nonionic dyes is associated with a two-thirds reduction of the risk for dye nephropathy among high-risk patients. This predominantly reflects milder renal hemodynamic alterations, but attenuated direct toxicity has been suggested as well.

Because intravenous hydration protocols and the use of low-osmolar and nonionic agents are time consuming and expensive, it is reasonable to suggest that they should be mandatory for high-risk patients, although cost-benefit implications may be taken into account for their application in low-risk individuals.

Other principal therapeutic interventions, currently considered experimental, have been directed at (1) the restoration of renal hemodynamics, (2) the improvement of medullary oxygenation by reduction of tubular transport, and (3) the amelioration of toxic damage. The reader is referred to a thorough review by Murphy et al, updated by some recent reports quoted later. It is noteworthy that most of these studies were performed in high-risk and well-hydrated patients who were given different classes of dye.

Restoration of Renal Hemodynamics

This approach has been studied extensively in experimental settings and in clinical trials among high-risk patients. Its logic is to reverse radiocontrast-induced decline in renal blood flow and GFR, thus washing out radiocontrast and removing obliterating tubular casts. L-arginine prevented a dye-associated decrease in renal blood flow and GFR in hypercholesterolemic animals, perhaps through the amelioration of endothelial dysfunction. The administration of dopamine increases renal blood flow, but its protective effects among high-risk patients have been inconsistent and perhaps deleterious among diabetic patients and during established contrast nephropathy. Conflicting results also characterize studies with the dopamine-1 receptor agonist fenoldapam, irrespective of whether the patients were diabetic. Prevention of dye nephropathy with theophylline also has been inconsistent, and data regarding the use of calcium-channel blockers are sparse. The effect of the ANP analogue anaritide was found to be absent or inconsistent, with a deleterious outcome in the diabetic subpopulation. The administration of a nonselective endothelin-receptor antagonist adversely affected the clinical outcome. However, animal studies indicate that selective endothelin-A receptor antagonists may have a protective effect.
probably underscoring the importance of endothelin-B receptor–mediated medullary vasodilation. Finally, the administration of prostaglandin E analogue may be beneficial, particularly after the use of nonsteroidal anti-inflammatory drugs, or in the aged population, characterized by defective renal prostaglandin synthesis.

On the whole, the inconsistent effect of renal vasodilators and the deleterious outcome in some subpopulations suggest that the potential beneficial outcome of enhanced cortical flow and GFR is counterbalanced by the enhancement of solute delivery for reabsorption in the distal nephron, which leads to intensification of outer-medullary hypoxia.

Reduction of Metabolic Workload

In uninephrectomized salt-depleted rats given indomethacin and radiocontrast, furosemide markedly attenuated hypoxic mTAL damage. However, kidney dysfunction was improved only modestly, probably reflecting the prerenal component of dehydration. When cosupplemented with saline, indices of dehydration resolved, and kidney function was preserved as well (see references 5 and 8 for a detailed bibliography). The rational of this approach is to prevent dye-associated medullary hypoxia. However, in 2 clinical studies by Solomon et al and by Weinstein et al, as compared with hydration protocol, hydration supplemented with furosemide adversely affected kidney function in high-risk patients given dye. Weinstein et al found that furosemide-treated subjects lost 0.7 kg on average, whereas a 1.3-kg weight gain was noted in patients randomized to hydration alone, suggesting that in furosemide-treated subjects the hydration protocol has been insufficient (see references 5 and 8 for a detailed bibliography). A lack of ameliorating effects of furosemide also might be expected in the aged population owing its failure to improve medullary oxygenation, determined non-invasive with BOLD magnetic resonance imaging. This may reflect diminished medullary activity of cyclooxygenase or nitric oxide synthase in this age group. It is noteworthy that, as shown by Solomon et al, kidney dysfunction after dye exposure in high-risk patients was more pronounced also in a mannitol-hydration group. As with furosemide, this also may be related to ensuing volume deficit, but in addition mannitol aggravates medullary hypoxemia owing to augmented distal tubular reabsorption, and may itself result in hypoxic acute tubular necrosis.

Measures to Attenuate Toxicity

N-acetylcysteine (NAC), given before and after radiocontrast studies, recently has been reported to improve renal outcome among high-risk well-hydrated patients. This finding was supported by some but not all subsequent clinical trials. In one of these studies, NAC-associated renal protection was restricted to patients given small volumes of dye. The beneficial effects of this agent have been attributed primarily to its antioxidant properties but as suggested by Safirstein et al, recent findings indicate that it also attenuates endothelial dysfunction and may improve renal hemodynamics after the administration of contrast. Nevertheless, an experimental model of dye nephropathy in rats subjected to coconcomitant inhibition of cyclooxygenase and nitric oxide synthase revealed an unexpected finding: renal dysfunction tended to be milder with NAC administration, but this was associated paradoxically with a trend toward enhanced tubular hypoxic damage. Again, this might imply that the beneficial effects of restoration of renal hemodynamics and tubular cytoprotection can be offset by the enhancement of reabsorptive workload that may increase medullary hypoxic damage.

CONCLUSIONS

Radiocontrast agents intensify medullary hypoxia. Experimental data and clinical characteristics of predisposing factors indicate that dye nephropathy is mediated predominantly by outer-medullary hypoxic tubular damage, probably combined with and accentuated by endothelial dysfunction and renal microcirculatory alterations. Tubular obstruction and direct toxic effect of the dye also may play a role. Therapeutic interventions directed at renal vasodilation and enhancement of GFR yield inconsistent results and may have deleterious effects, particularly among diabetic patients, perhaps reflecting further intensification of medullary hypoxemia. Furosemide, given to improve medullary hypoxemia, adversely affected renal function, perhaps owing to ensuing dehydration. Noninvasive technologies, such as positron emission tomography and BOLD magnetic resonance imaging are critically needed for the real-time determination of intrarenal oxygenation and metabolic status. With
such technologies available we may better understand the relative contribution of hypoxia and altered renal microcirculation. Such technical progress may enable a more logical therapeutic approach (ie, to improve hemodynamics or to reduce metabolic activity).

Proper selection of patients, elimination of concurrent use of nephrotoxic agents, appropriate hydration, and the use of low osmolar and nonionic dye in high-risk patients at the lowest volumes required are currently the only proven preventive measures. It is conceivable that to further reduce the risk for dye nephropathy in high-risk patients, combined strategies should be tested. Suggested combinations are the inhibition of tubular transport by loop diuretic (with sufficient fluid replacement), in addition to agents that improve renal microcirculation (theophylline, fenoldopam, prostaglandin E analogues, L-arginine, or endothelin-A receptor antagonists), perhaps combined with NAC, which might provide additional vasodilatory and cytoprotective effects.

REFERENCES