Contrast Agent Induced Nephropathy Following Computed Tomography in Patients with Advanced Chronic Kidney Disease: Myth or Reality?

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ABSTRACT Recent studies using propensity score matching have clearly indicated that contrast nephropathy following computed tomography occurs in hospitalized patients with advanced chronic kidney disease (eGFR < 30 ml/min/1.73 m^2) and that this iatrogenic complication is likely underestimated because of concomitant renal functional recovery, unrelated to the imaging procedure. These findings should be considered regarding contrast-enhanced studies in such patients.

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KEY WORDS: acute renal failure, chronic kidney disease (CKD), computed tomography (CT), radiocontrast agents, renal functional reserve

Contrast-enhanced computed tomography (CT) is widely used in many clinical fields. Yet, the administration of iodine-based contrast agents raises concerns regarding the risk of contrast-induced nephropathy (CIN), defined most often as rising serum creatinine of > 0.3 mg/dl or 1.5 times the baseline levels within 48 hours after contrast-enhanced imaging [1]. For years, advanced chronic kidney disease (CKD) and diabetes have been considered as principal patient-related risk factors predisposing CIN, followed by aging, hypovolemia, heart failure, and anemia [2]. This concern requires tough decisions when it comes to the diagnosis of life-threatening conditions in high-risk patients, as contrast-enhanced CT is considered the diagnostic gold standard. In a recent clinical decision debate article in the *New England Journal of Medicine*, Lee et al. [3] discussed the use of contrast-enhanced CT for the diagnosis of pulmonary emboli in a diabetic patient with stage 4 CKD. The principal dispute addressed the true risk of CIN compared to the need to diagnose or to exclude this life threatening treatable medical condition. To some extent, the dispute was vague regarding the risk of CIN following CT versus the use of alternative diagnostic options. In this review, we contributed to this debate based on our basic research findings and clinical observations.

CONTRAST NEPHROPATHY FOLLOWING COMPUTED TOMOGRAPHY CAN OCCUR. IT EXISTS IN PATIENTS WITH ADVANCED CHRONIC RENAL DISEASE WITH EGFR < 30 ml/min/1.73 m^2.

Iodine-based contrast agents exert profound changes in renal microcirculation, tubular transport, and parenchymal oxygenation, which may lead to oxidative stress and hypoxic injury, especially affecting the outer medulla [4]. Increased plasma and urine levels of biomarkers of medullary tubular injury were noted in children with congenital heart disease undergoing cardiac catheterization who developed CIN [5]. The currently used low-osmolar ionic, iso-osmolar ionic, or non-ionic agents are substantially less nephrotoxic than the high-osmolar older compounds. Nevertheless, the volume of injected contrast agents remains a major determinant in the risk to develop CIN [6]. The risk of CIN is undisputable in patients subjected to large volumes of the newer contrast agents required for vascular interventions [7]. However, a small amount of contrast material is needed for CT, which reduces or eliminates the risk of CIN [8-11], leading to the belief that CIN following contrast-enhanced CT is a myth rather than a true issue [12]. We concur regarding the safety of contrast-enhanced CT based on large data analysis of patients who underwent this procedure, even after correcting for numerous confounding variables [13,14]. Yet, a meticulous subsequent analysis revealed unequivocally that advanced CKD with eGFR < 30 ml/min/1.73 m^2 remains an important risk factor for CIN, increasing the likelihood of post-contrast acute kidney injury (AKI) by 59% compared to patients with advanced CKD subjected to non-enhanced CT [15]. Our findings follow those of Davenport and colleagues [16], who also conducted big data analysis with propensity matching and found increasing odds of CIN reaching 1.4 and 3 at eGFR < 44 ml/min/1.73 m^2 and < 30 ml/min/1.73 m^2, respectively. We found that the true incidence of CIN may be substantially underestimated by incidental concomitant recovery of kidney function (acute kidney functional recovery [AKR]), unrelated to the imaging

procedure [17]. AKR, which occurs three times as often as AKI among patients, likely reflects the impact of patient management during hospitalization, including hydration protocols, control of infections, hemodynamic and metabolic stabilization, and improved respiratory status. Interestingly, AKI and AKR closely co-associate along the scale of baseline serum creatinine and are proportional to the decline in kidney function, suggesting that both reflect diminished renal functional reserve [18]. Thus, the predisposition of patients with advanced CKD to develop AKI following various insults, including the exposure to contrast agents, might reflect the loss of the blunting impact of renal functional reserve as renal functional mass declines [19]. The patient discussed in the vignette by Lee et al. [3] presented with diabetes, an additional factor predisposing to CIN [4] since it intensifies hypoxic and oxidative stress induced by the contrast material [20]. Furthermore, hyperglycemia in diabetics is characterized by increased incidence of AKR during hospitalization in proportion to blood glucose levels upon admission [21], which could further conceal the true incidence of CIN. Thus, we believe that AKI following contrast-enhanced CT remains an important iatrogenic complication in specific patients, which is masked by renal functional reserve and by measures that stabilize renal function along the hospitalization course, irrespective to the imaging procedure.

RENAL FUNCTION IS OFTEN COMPROMISED IN PATIENTS HOSPITALIZED WITH AN ACUTE ILLNESS. RENAL FUNCTIONAL RECOVERY DURING HOSPITALIZATION COMMONLY OCCURS IN SUCH SETTINGS AND CONTRIBUTES TO THE UNDERESTIMATION OF THE TRUE INCIDENCE OF CONTRAST NEPHROPATHY.

THE RISK OF CONTRAST NEPHROPATHY SHOULD BE CONSIDERED DURING CONTRAST-ENHANCED STUDIES IN PATIENTS WITH ADVANCED KIDNEY DISEASE.

In addition to these clinical and physiologic confounders, flawed data likely contribute to the confusion regarding the true risk of CIN following contrast-enhance CT. Even prospective and controlled studies likely are biased by inappropriate matching and a plausible selection bias of patients because the unenhanced CT group may include patients who are at risk for AKI. Furthermore, the relatively low risk of CIN following contrast-enhanced CT requires large numbers of patients to determine risk evaluation, with numbers achieved by meta-analyses with combined databases often incomplete and non-homogenous. Our insight regarding the true risk of AKI in general and specifically of CIN in hospitalized patients with advanced CKD is likely robust as it stems from big data analyses of patients subjected to standardized imaging protocols [13,15-17,21], implementing propensity score matching that controls for numerous available demographic and clinical parameters [22].

Based on the case discussed by Lee et al. [3], we favor performing first Doppler ultrasonography for high-risk patients with advanced CKD, especially those with diabetes, without exposing them to contrast material if deep vein thrombosis is detected. We believe that this bedside technology should be available with practiced medical professionals in all departments of emergency services [23]. Other diagnostic tools, such as cardiac echocardiography or perfusion lung scan, may also be helpful. The small details of medical history and physical findings, ignored in the vignette [3], are also invaluable in constructing gut feelings regarding operative decisions that consider perceived pre-test probabilities and risk-benefit ratios. By contrast, determination of plasma D-dimer in the vignette is valueless in patients with advanced CKD as its elimination is through renal clearance.

CONCLUSIONS

The Lee case [3] showed that although contrast-enhanced CT is an excellent and invaluable diagnostic tool for a variety of conditions including thromboembolism, CIN following this procedure in patients with advanced CKD is definitely a possibility. In such patients, the diagnostic yield of contrast-enhanced tomography should be weighed against the risk of CIN. Efforts should be made to minimize the risk of CIN by utilizing technologies that might help diagnosis without the need of contrast-enhanced CT, as outlined in the European Society of Urogenital Radiology and the American College of Radiology safety guidelines [24,25].

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Capsule

Replenishment of self-renewing T cells

Stem-like CD8 T cells develop during periods of persistent antigen exposure. During chronic infection and cancer, therapies can stimulate the differentiation of antigen-specific stem-like CD8 T cells into cells with effector function. However, factors controlling the integrity of the stem-like T cell pool have been unknown. Studying chronic viral infection in mice, **Humblin** co-authors found that the costimulatory molecule CD28 regulated the metabolism of stem-like CD8 T cells expressing the inhibitory receptor PD-1 to promote self-renewal and differentiation. In companion work, **Gill** and colleagues found that anti–PD-1 blockade, while promoting effector cell differentiation, likewise stimulated the self-renewal of these stem-like T cells, maintaining the size and functionality of the progenitor pool. Thus, immune checkpoint therapies may rejuvenate immune responses without diminishing the durability of the stem-like T cells that respond to treatment.

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Capsule

Immune cells maintain human colon health

Inflammatory bowel disease (IBD) refers to two conditions: Crohn's disease and ulcerative colitis. Individuals with IBD have chronic intestinal inflammation in which the intestinal epithelial barrier is disrupted. **Dart** and colleagues examined human colon biopsy samples and identified intestinal immune cells called Vγ4 γδ T lymphocytes. In healthy individuals, this γδ T cell subset is kept in check by intestinal epithelial cells displaying the butyrophilin-like (BTNL) proteins BTNL3 and BTNL8. By contrast, analysis of biopsies from Crohn's disease patients revealed a polymorphism encoding a defective BTNL3:BTNL8 fusion protein, and this genetic mutation was correlated with IBD severity. These findings increase our understanding of barrier immunology and may provide new perspectives for IBD management.

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