Contrast-induced nephropathy (CIN) is a common complication of coronary angiography and percutaneous coronary intervention, and is associated with prolonged hospitalization and worsening of clinical outcomes. CIN is defined as an increase in creatinine levels by ≥0.5 mg/dl or ≥25% from baseline within 72h after contrast radiography using iodinated contrast media.

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In this issue of the Journal, Saito et al identify proteinuria as an independent risk factor for CIN in patients who underwent cardiac catheterization. Because few studies have examined the clinical significance of proteinuria as a risk factor for CIN after cardiac catheterization until the publication of Saito’s findings, proteinuria was not considered as a candidate risk factor for CIN in one of the most ambitious strategic studies by Mehran et al. Furthermore, the finding that the incidence of CIN in patients with proteinuria markedly increased, especially in patients with a severely reduced glomerular filtration rate, may be important information for attending physicians.

Why is proteinuria an independent risk factor for CIN? The over-reabsorption of albumin in proximal tubular cells has been reported to upregulate some mediators such as endothelin-1, monocyte chemotactic protein-1 (MCP-1), interleukin-8, and RANTES, resulting in renal cell proliferation, activation of macrophages and monocytes, deposition of matrix, and ultimately, tubulointerstitial damage. Other studies using an experimental model of progressive proteinuric nephropathy caused by 5/6 nephrectomy or passive Heymann nephritis showed that proteinuria primarily led to interstitial inflammation via the upregulation of NF-κB or MCP-1. Furthermore, as a consequence of proteinuria, the intrarenal activation of the complement cascade may promote injury through the formation of a membrane attack complex and biologically active products, such as C3a or C5b-9, which have been shown to interact with specific receptors that are strongly expressed by kidney epithelial cells and mediate altered gene expression, thereby enhancing extracellular matrix deposition. These events ultimately lead to tubulointerstitial inflammation and fibrosis in the long-standing proteinuric nephropathy. Because patients with documented proteinuria have compromised physiological adaptability and are less able to tolerate kidney hemodynamic changes and other nephrotoxic insults, proteinuria may be a risk factor for dialysis-requiring acute renal failure (Figure).[1]

On the other hand, the mechanisms underlying CIN have been described. After inducing a brief period (several minutes) of endothelial-independent transient vasoconstriction, iodinate contrast causes sustained (several hours) intrarenal vasoconstriction because of the release of adenosine, endothelin, and other renal vasoconstrictors. Sustained intrarenal vasoconstriction then leads to reductions in renal blood flow that last for several hours, resulting in a persistent nephrogram, which is a powerful indicator of CIN in patients who have undergone an emergency coronary procedure.[2] The stasis of contrast medium in the kidney causes direct cellular injury and death of renal tubular cells because the degree of cytotoxicity to renal tubular cells is directly related to the length of exposure these cells have to iodinated contrast. Thus, isotonic hydration resulting in high urinary flow rates before, during, and after contrast procedures has been reported to prevent CIN.[3] Sustained reductions in renal blood flow to the outer medulla also lead to medullary hypoxia, ischemic injury, and the death of renal tubular cells. Thus, increased contrast exposure in renal tubular cells and medullary hypoxia directly induces cellular injury and death, as well as ischemic injury, through the activation of oxidative stress, inflammation, and other organ injury processes. Therefore, iodinated contrast may be one of the nephrotoxic insults resulting in CIN, especially in patients with proteinuria who have compromised physiological adaptability and are less able to tolerate iodinated contrast (Figure).

The precise mechanism underlying CIN has not yet been elucidated in detail; therefore, specific effective strategies for the treatment of CIN are limited, whereas several preventive measures have been reported to reduce the risk of CIN. Lower doses of contrast, avoidance of repetitive contrast studies, avoidance of volume depletion or nonsteroidal antiinflammatory drugs, administration of intravenous saline or sodium bicarbonate, administration of acetylcysteine, and use of selected low- or iso-osmolar nonionic contrast agents need to be considered as measures to prevent CIN. However, because the preventive effects of these measures for CIN have not been evaluated, especially in patients with proteinuria, further studies are needed.

Disclosures

None.

References