Pathophysiology of Contrast-Induced Acute Kidney Injury

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KEYWORDS

• Contrast media adverse effects • Contrast media toxicity • Contrast-induced nephropathy
• Contrast-induced acute kidney injury

KEY POINTS

- Ten percent of the renal blood flow represents medullary flow.
- P_{O_2} levels of the medulla can be as low as 20 mm Hg.
- Blood supply to the medulla is derived from the efferent arterioles, which give rise to the descending vasa recta (DVR) at the corticomedullary junction.
- Contrast media (CM) cause medullary hypoxia by hemodynamic effects, an increase in oxygen free radicals, and direct CM molecule tubular cell toxicity.
- Points of action for CM to cause vasoconstriction seem to be the afferent arterioles and the DVR.
- Both medullary ischemia and tubular cell toxicity lead to increased formation of oxygen free radicals.
- Increased formation of oxygen free radicals leads to increased ischemia and cell toxicity.
- Therefore, the 3 pathways of contrast-induced acute kidney injury enhance and support each other.

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) refers to acute kidney injury (AKI) after intravenous or intra-arterial administration of contrast media (CM). The 2 key mechanisms related to AKI are acute tubular necrosis and prerenal azotemia, that is, increased serum creatinine and urea resulting from kidney hypoperfusion.[1] The pathophysiology of AKI in general is complex, and most of the understanding of this condition comes from animal studies. Modern frameworks show that AKI has 3 major pathways: hemodynamic injury, systemic inflammation, and toxic injury.[1] Among the potentially nephrotoxic drugs, CM are prominent.[1] In the pathophysiology of CI-AKI, 3 major distinct, but potentially interacting pathways are recognized: hemodynamic effects, increase in oxygen free radicals, and direct CM molecule tubular cell toxicity.[2] This article reviews the pathophysiology of CI-AKI by describing and explaining these pathways.

DIRECT CM MOLECULE TUBULAR CELL TOXICITY

Of the 3 pathways, the contribution of direct tubular cell toxicity caused by CM is the least understood. All types of CM, high-osmolar, low-osmolar, and iso-osmolar, display toxicity in

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in vitro studies of tubular cell cultures.[3] What exactly happens when CM come into contact with renal tubular cells in vivo is unknown. In general, the toxic effects of high-osmolar CM are more pronounced than the effects of low-osmolar or isoosmolar CM, but all types of CM have negative effects on cell cultures.[3,4] Many toxic effects of CM on renal cell cultures have been described: apoptosis, redistribution of membrane proteins, reduction of extracellular Ca^{2+}, DNA fragmentation, disruption of intercellular junctions, reduced cell proliferation, and altered mitochondrial function.[3,4] Apoptosis especially has been associated with increased levels of oxygen free radicals,[3] underlining how cell toxicity and formation of oxygen free radicals enhance each other. Furthermore, iodine is well known for its cytotoxic effect on bacteria, but is also toxic to human cells.[4] To what degree the small amount of free iodine in CM solutions is responsible for tubular cell toxicity remains unknown.

OXYGEN FREE RADICALS

Oxygen free radicals are molecules that contain 1 or more unpaired electrons, such as superoxide (O_2^-) and hydroxyl radical (OH^-).[2,5] During successive reduction reactions, these highly reactive molecules are turned into water.[2] Less aggressively reacting molecules, such as H_2O_2, are called reactive oxygen species (ROS).[2,5] In the pathophysiology of CI-AKI these types of molecules play a key role, as they interact with the other 2 pathways. Once formed during hypoxia and/or cellular injury and exceeding the cellular scavenging capacities, they lead to a specific type of injury, the so-called ischemia/reperfusion injury.[6] This type of cellular injury is a combination of both hypoxia and oxidative damage.[6]

Hypoxia is due to alteration of the renal microcirculation induced by oxygen free radicals and ROS. The exact pathway by which these molecules act on renal vasoconstrictors and vasodilators is unknown, but oxygen free radicals and ROS trigger an increase in vasoconstriction induced by angiotensin II and endothelin I.[6] Furthermore, they reduce the bioavailability of the vasodilative nitric oxide (NO),[6] eventually leading to increased renal vasoconstriction. As CM administration already decreases medullary blood flow and increases the oxygen demand of renal tubular cells, this medullary ischemia is increased by the formation of oxygen free radicals and ROS. On the other hand, ischemia leads to increased formation of -oxygen free radicals and ROS, so both processes enhance each other.

Oxidative damage to cells is due to the oxidative stress of highly reactive molecules. Intracellularly an imbalance between oxidants and antioxidants occurs, in favor of the oxidants. This imbalance affects mitochondrial and nuclear DNA, membrane lipids, and cellular proteins.[6] The result is increased cell injury leading to increased formation of oxygen free radicals and ROS, creating a vicious cycle.

HEMODYNAMIC EFFECTS

Besides hemodynamic renal effects caused by cell toxicity and increased oxidative stress, CM also have a direct effect on the renal vasculature.

Under physiologic resting conditions, 25% of the cardiac output is directed toward the kidneys. The greater part of cardiac output is directed toward the cortex, to optimize glomerular filtration and reabsorption of water and salts.[7] The medullary blood flow is low; 10% of the renal blood flow represents medullary flow.[8] Its function is to preserve osmotic gradients and enhance urinary concentration.[7] Under physiologic circumstances, oxygen partial pressure (P_{O_2}) levels of the renal cortex are approximately 50 mm Hg, whereas P_{O_2} levels of the renal medulla can be as low as 20 mm Hg (**Fig. 1**).[7,9] The most vulnerable part of hypoxic damage is the deeper portion of the outer medulla that contains the metabolically active thick ascending limbs of the loop of Henle. In this part of the tubular system, an osmotic gradient is generated by active reabsorption of sodium, a process that requires a relatively large amount of oxygen.[7]

Blood flow to the renal medulla is derived from efferent arterioles of juxtamedullary glomeruli. At the corticomedullary junction, these efferent arterioles give rise to the so-called descending vasa recta (DVR). These DVR gradually form a capillary bed that penetrates deep into the inner medulla. These capillaries eventually coalesce to form ascending vasa recta (AVR) (**Fig. 2**). The transformation from DVR to capillaries and thence to AVR occurs gradually, with accompanying histologic changes in the composition of the vessel wall.[10]

After intravascular administration, CM display a rapid distribution over intravascular and extracellular fluids. The distribution half-life is usually several minutes, ranging from 2 to 30 minutes. Only 1% to 3% is bound by plasma proteins.[11]

Metabolism of CM in the human body does not take place. CM are eliminated quickly through glomerular filtration by the kidneys. The elimination half-life, or time to clear half of the amount of CM in the blood, is approximately 1 to 2 hours.[11] In the