JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 68, NO. 13, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.05.099

REVIEW TOPIC OF THE WEEK

Contrast-Induced Acute Kidney Injury

Peter A. McCullough, MD, MPH,[a,b,c,d] James P. Choi, MD,[c] Georges A. Feghali, MD,[c] Jeffrey M. Schussler, MD,[c] Robert M. Stoler, MD,[c] Ravi C. Vallabahn, MD,[c] Ankit Mehta, MD[a]

ABSTRACT

Coronary angiography and percutaneous intervention rely on the use of iodinated intravascular contrast for vessel and chamber imaging. Despite advancements in imaging and interventional techniques, iodinated contrast continues to pose a risk of contrast-induced acute kidney injury (CI-AKI) for a subgroup of patients at risk for this complication. There has been a consistent and graded signal of risk for associated outcomes including need for renal replacement therapy, rehospitalization, and death, according to the incidence and severity of CI-AKI. This paper reviews the epidemiology, pathophysiology, prognosis, and management of CI-AKI as it applies to the cardiac catheterization laboratory.
(J Am Coll Cardiol 2016;68:1465–73) © 2016 by the American College of Cardiology Foundation.

There have been many advancements in the field of interventional cardiology that have resulted in a greater degree of patient safety and have allowed an ever-increasing population at risk to undergo diagnostic and interventional procedures. Despite these steps forward, accurate imaging of the coronary and peripheral vasculature remains dependent on the use of intravascular injection of iodinated contrast, which has well-known toxicities, including contrast-induced acute kidney injury (CI-AKI). This paper presents an update on the epidemiology, pathogenesis, prognosis, and management of CI-AKI as applied specifically to cardiac interventional procedures.

EPIDEMIOLOGY

There are considerable sources of information indicating that CI-AKI, and perhaps AKI overall, in patients undergoing cardiac catheterization procedures has been declining over the past decade or more. However, among those undergoing cardiac surgery after coronary angiography, AKI and AKI requiring dialysis (AKI-D) may be increasing. In 2012, Amin et al. (1) reported on 33,249 hospitalizations for acute myocardial infarction in the United States of 31,532 patients and demonstrated that the rate of AKI declined from 26.6% in 2000 to 19.7% in 2008 (26% reduction) using a definition consistent with the Kidney Disease International Global Outcomes Guidelines of a rise in serum creatinine (sCr) ≥0.3 mg/dl or a ≥50% elevation from baseline over the course of hospitalization. The National Cardiovascular Data Registry Cath-PCI (N = 985,737 who underwent elective and urgent percutaneous coronary intervention [PCI]) reported 69,658 (7.1%) cases of CI-AKI (sCr rise ≥0.3 mg/dl) and 3,005 (0.3%) cases of AKI-D (**Figure 1**) (2). Although in **Figure 1**, estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 is indicated to be normal, it may not be the case if it is in the setting of a unilateral kidney or in a patient with structural kidney disease (e.g., polycystic kidney disease). As chronic kidney disease (CKD) progresses and eGFR worsens, there is a sharp increase in the rates of both CI-AKI and AKI-D, as shown in **Figure 1**. The most important factors associated with a more than doubling in the rates of CI-AKI and significant increases in the risk of AKI-D were ST-segment elevation myocardial infarction (STEMI), eGFR <30 ml/min/1.73 m^2, and cardiogenic shock. Mean

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Internal Medicine, Division of Cardiology, Baylor University Medical Center, Dallas, Texas; [b]Baylor Heart and Vascular Institute, Dallas, Texas; [c]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Texas; and [d]The Heart Hospital Baylor Plano, Plano, Texas. Dr. Stoler is on the advisory boards of Boston Scientific and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 1, 2015; revised manuscript received April 20, 2016, accepted May 3, 2016.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-enzyme inhibitor

ACS = acute coronary syndromes

AKI-D = acute kidney injury requiring dialysis

ARB = angiotensin-receptor blocker

CI = confidence interval

CI-AKI = contrast-induced acute kidney injury

CKD = chronic kidney disease

Cr = creatinine

eGFR = estimated glomerular filtration rate

ESRD = end-stage renal disease

HF = heart failure

HR = hazard ratio

LVEDP = left ventricular end-diastolic pressure

MI = myocardial infarction

PCI = percutaneous coronary intervention

RASi = renin-angiotensin system inhibitors

sCr = serum creatinine

STEMI = ST-segment elevation myocardial infarction

TAVR = transcatheter aortic valve replacement

contrast volumes among those with CI-AKI ranged from 140 to 260 ml, similar to those without CI-AKI (140 to 245 ml). Thus, although rates of CI-AKI may have historically trended down over the past decade, the risk is still formidable in the patients with the greatest need for urgent PCI, including those with STEMI and those developing cardiogenic shock. In addition, the overall age in this report from the Cath-PCI registry is 64.8 ± 12.2 years and thus is not reflective of the growing numbers of the elderly undergoing PCI currently and in the future. As the Cath-PCI registry report elucidated, baseline eGFR, STEMI, and cardiogenic shock are strong predictors of CI-AKI and AKI-D after PCI. Mehran et al. (3) developed and validated a comprehensive risk prediction score, which also included age, hemoglobin, pre-existing CKD, contrast volume, need for intra-aortic balloon counterpulsation, and other variables, in order to anticipate the rate of CI-AKI, as well as the need for renal replacement therapy. Although this tool can be used for quality reporting and other functions, it is not helpful before the procedure because it incorporates variables that can only be known after the case is completed in the catheterization laboratory. For pre-procedural counseling, the most useful parameters are the eGFR and presence of diabetes. In general, eGFR <60 ml/min/1.73 m^2 with diabetes elevates the risk of CI-AKI sufficiently above the baseline of ~5% to ~10%; thus, appropriate counseling and preventive measures are warranted to mitigate this potential adverse consequence of angiography.

PATHOPHYSIOLOGY

All forms of iodinated contrast are highly water-soluble carbon-based benzene rings that exist as monomers with 3 iodine atoms attached or as dimers with 6 iodine atoms attached. The most common types of contrast agents used today for intravascular injection are either iso-osmolar (approximately 290 mOsm/kg) iodixanol, which is a dimer, or low-osmolar (700 to 850 mOsm/kg) nonionic monomers (iohexol, iomeprol, iopamidol, iopromide, ioversol, ioxilan) (4). High-osmolar contrast agents (1,200 mOsm/kg or higher) are no longer used for cardiac catheterization. The iodine concentration of these products is similar (320 to 270 mg I/ml). However, when administered in the blood at 37°C, the 11.8 centipoise (cps) viscosity of iodixanol is significantly higher than that of iohexol, at 6.3 cps, the lowest in the low-osmolar category. In a rat model, the viscosity in urine can be considerably greater with iodixanol (5). Among these 3 physiochemical properties, the higher the osmolality or the particle concentration in solution, the greater the vascular symptoms of warmth and pain during injection, as well as CI-AKI (6). When iodinated contrast is injected into the systemic arterial circuit, there is a transient endothelium-dependent vasodilation mediated by release of nitric oxide, followed by arteriolar vasoconstriction lasting for several seconds to minutes in the peripheral circulation (**Figure 2**) (7). In the renal arcade of blood vessels that subdivide into the afferent glomerular arteriole serving the glomerulus, efferent arteriole dividing and forming the peritubular network, and finally the vasa recta, the transient dilation can be followed by a period of sustained vasoconstriction that lasts for several hours (7). When there is a reduced renal parenchymal mass and fewer nephrons in the setting of CKD and among those with diabetes, the reduction in renal blood flow can be sufficiently sustained to impair oxygenation to the outer medulla, resulting in ischemia to the proximal and distal tubules. Furthermore, the water-soluble contrast is readily taken up by the apical surface of proximal tubular cells (pumps, bystander endocytosis) and out of the basal-lateral surface into the tubulointerstitial space (8). Tubular cells undergo swelling, blebbing, and apoptosis, as shown in **Figure 2**. As a result, there is stasis of contrast within the kidneys after the procedure is completed. Of note, 3-hydroxy-3-methyl-glutaryl-CoA reductase regulates the production of isoprenoid pyrophosphates, which in turn play a key role in the proper function of guanosine triphosphate-binding protein-mediated endocytosis (9). In an in vitro model, statins inhibit endocytosis in renal tubular cells (10). This is the putative, beneficial mechanism of action attributed to statins, which will be discussed later. With high concentrations of contrast within and surrounding renal tubular cells, there is direct cellular toxicity with loss of the tubular brush border, breakdown of desmosomes, loss of cell membrane integrity, and sloughing of material into the urinary tubular space (Tamm-Horshfall protein), which promotes further stasis of contrast in the urine, enabling more movement of contrast into the tubulointerstitial space, where there is no ready form of clearance. Patients with CKD and diabetes have been reported to have persistent nephrograms where contrast can be seen within the kidneys for up to 8 days after contrast administration (11). The