Contrast-induced acute kidney injury

Lesão renal aguda induzida por contraste

Gustavo Neves de Araujo1, Mateus Lech2, Rodrigo Vugman Wainstein1, Marco Vugman Wainstein1

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ABSTRACT – Contrast-induced acute kidney injury is not a rare event after exposure to contrast media, and affects approximately 1 to 2% of patients in general radiological imaging procedures. The incidence of contrast-induced acute kidney injury is even higher among patients undergoing percutaneous coronary intervention, and ranges from 3 to 19% according to the patient’s risk profile. It is associated with increased morbidity, mortality, hospital length-of-stay and healthcare costs. Hence, since there is no targeted treatment after its onset, identifying high risk patients and preventing its occurrence is of paramount importance to avoid adverse outcomes after percutaneous coronary intervention.

Keywords: Contrast media; Acute kidney injury; Percutaneous coronary intervention

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is not a rare event after exposure to contrast media, and affects roughly 1 to 2% of patients in general radiological imaging procedures.1 CI-AKI incidence is even higher among patients undergoing percutaneous coronary intervention (PCI), and ranges from 3 to 19% according to the patient’s risk profile.2-4 CI-AKI is associated with increased morbidity, mortality, hospital length-of-stay and healthcare costs.3 Hence, since there is no targeted treatment after its onset, identifying high risk patients and preventing its occurrence is of paramount importance to avoid adverse outcomes after PCI. Summarized information on CI-AKI is shown in figure 1.

Definition
A rise of 0.3mg/dL or 50% in 48 to 72 hours post-procedure creatinine compared to baseline

Pathophysiology
Afferent vasoconstriction and direct tubular damage

Risk factors
Related to previous kidney perfusion and nephrotoxicity

Clinical implications
Increased risk of bleeding, dialysis, stroke, myocardial infarction and mortality

Prevention
Identify high risk patients, avoid high volume of contrast, hydration protocols, avoid concomitant nephrotoxic agents

Figure 1. Summarized information on contrast-induced acute kidney injury.
PATHOPHYSIOLOGY

The pathophysiology of contrast-induced nephropathy (CIN) is complex, multifactorial and only partially understood (Figure 2). The implicated mechanisms are associated with afferent arterioles vasoconstriction and direct tubular damage caused by iodinated contrast media (ICM), but some clinical aspects, such as hemodynamic instability, cholesterol embolism to the kidney, and concomitant drug toxicity can potentiate CIN development and severity.

Iodinated contrast media are water soluble carbon-based benzene rings used in interventional radiology to obtain vessel and chamber imaging. ICM causes a direct toxic effect on renal tubular cells by exposing them to high osmotic load, inducing impairment in intracellular transport and energy metabolism, and leading to cytopathological changes ranging from tubular cell vacuolisation to necrosis. Increased renal interstitial pressure after exposure to contrast media also plays a role in the pathophysiology of CIN, since raised interstitial pressure may compress the microcirculation of the vasa recta, resulting in medullary hypoxia and CIN.6

When iodinated contrast is injected into the systemic arterial circuit, there is a transient endothelium-dependent vasodilation mediated by release of nitric oxide (NO), followed by arteriolar vasoconstriction, lasting from seconds to hours. NO causes a release of reactive oxygen species, leading to a reduction in partial pressure of arterial oxygen (PaO₂) and increased vascular reactivity to various vasoconstrictors, such as norepinephrine, angiotensin II, endothelin and adenosine. In humans, total renal blood flow may be reduced by up to 50% after the injection of ICM.7 The persistent decline in glomerular filtration that follows ICM administration also results in an increased generation of reactive oxygen species.8

The reduction in renal blood flow affects particularly the outer medulla, which is more susceptible to ischemia and apoptosis of the tubular cells due to its high metabolic activity. Since there is no glomerular injury, hematuria is not present. Oliguria is also not expected in CI-AKI. Subclinical kidney injury occurs in virtually every patient exposed to iodinated contrast; however, because there is a robust tubular repair capability in healthy subjects, clinically relevant CI-AKI only occurs in predisposed patients who are unable to rapidly repair tubular damage.

A less common cause of kidney injury after PCI is cholesterol embolism. Considering that the kidneys receive 25% of cardiac output, microshowers of atheroembolic material may deposit in the renal tissue after PCI. Cholesterol embolization syndrome (affecting different organs) occurs in up to 1.4% of patients undergoing cardiac catheterization.9 However, a series of autopsies in patients who died within 6 months after arteriography procedures showed that subclinical embolization can be seen in up to 30% of cases.10

Figure 2. Pathophysiology of contrast-induced acute kidney injury in patients with and/or without myocardial infarction.
DEFINITION AND DIAGNOSIS

The most contemporary CI-AKI definition is a rise of 0.3mg/dL or 50% in creatinine, 48 to 72 hours after the procedure, as compared to baseline values. The increase in post-procedure creatinine, however, has been controversial. Definitions range from a more restrictive (i.e., an increase >1.0mg/dL in creatinine above baseline) to a more sensitive criteria (i.e., an increase of creatinine > 25% above baseline), which leads to a wide variation in its incidence (2% in restrictive11 and 12.3% in sensitive criteria15), and short- and long-term prognostic value after CI-AKI development. Harjai et al.13 compared different definitions of CI-AKI, and found that a more restrictive criteria fails to identify a large amount of patients with smaller increases in creatinine, leading to underestimation of the incidence of CI-AKI and failing to predict adverse events. In this study, a rise in serum creatinine ≥0.5mg/dL and/or ≥25% within 72 hours after PCI was predictive of 6-month major adverse cardiovascular events (MACE) and all-cause mortality after PCI. Although several studies used the latter definition14,15 growing data suggested that CI-AKI identification could be improved.

In 2007, the Acute Kidney Injury Network (AKIN) suggested a novel CI-AKI definition in order to standardize AKI assessment and classification in everyday clinical practice, as well as in research conditions.16 CI-AKI was defined as a rise of creatinine 48 to 72 hours after procedure higher than 0.3mg/dL or 50% compared to baseline. The absolute criteria for the diagnosis of CI-AKI were based on the emerging knowledge that even small variations in creatinine levels are associated with higher morbidity and mortality rates. Centola et al. confirmed that AKIN definition provides a better accuracy in predicting long-term mortality compared to a rise in serum creatinine ≥0.5mg/dL and/or ≥25% within 72 hours after PCI.17 Using a definition that correlates better with hard outcomes seems reasonable, since reducing CI-AKI may potentially reduce these outcomes.

EPIDEMIOLOGY

The incidence of CI-AKI is highly variable in literature. It depends on procedure type, contrast load, clinical presentation (i.e. primary vs. elective PCI), population characteristics and CI-AKI definition, which is not uniform, as commented.

In hospitalized patients, contrast medium exposure after radiological imaging procedures is related to the development of acute kidney injury in approximately 1% of cases.1 According to the National Cardiovascular Data Registry (NCDR®), 7.1% of 985,737 patients undergoing elective and urgent PCI developed CI-AKI (AKIN definition), and 0.3% (n=3005) required new dialysis.18 While CI-AKI was complicated in 4.4% of elective cases, it was observed in 7.9% of patients after acute coronary syndromes, in 10.9% of patients after ST-elevation myocardial infarction (STEMI) and in 36.9% of chronic renal disease (CKD) patients presenting with STEMI. In an Italian registry, the incidence of CI-AKI was 14% in patients hospitalized with acute coronary syndromes;19 the same authors had previously found an incidence of 19% using a different CI-AKI definition.2

RISK FACTORS

The risk factors for CI-AKI are mainly related to previous kidney dysfunction, current nephrotoxicity and potential kidney malperfusion, and can be classified into modifiable and non-modifiable risk factors (Chart 1). Patients with pre-existing kidney disease are unable to rapidly correct tubular damage, potentially leading to CI-AKI. CI-AKI risk is directly related to baseline glomerular filtration rate (Table 1).18 Age is a risk due to natural loss of tubular function, but also because of more difficult vascular access requiring greater amount of contrast, presence of multivessel disease, and comorbidities. Diabetic patients more often present renal dysfunction, as well as a higher risk of vascular disease. Anemia leads to reduced kidney perfusion, and to cardiac risk factors, such as heart failure, cardiogenic shock and use of intra-aortic balloon pump. Acute coronary syndromes increase the risk of CI-AKI due to a multifactorial mechanism, including kidney damage by inflammatory cytokines and kidney hypoperfusion. Use of other nephrotoxic medications, such as nonsteroidal anti-inflammatory drugs, also increase the risk of CI-AKI.

Contrast media is nephrotoxic, thus the risk of CI-AKI is dose-related. However, CI-AKI is unlikely in patients receiving less than 100mL of volume.20 Increasing complexity of coronary intervention leads to higher volumes of contrast,

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
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<tbody>
<tr>
<td>Age</td>
<td>Anemia</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Contrast volume</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Contrast osmolality*</td>
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<td>Acute coronary syndromes</td>
<td>Cardiogenic shock</td>
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<td>Pre-existing kidney disease</td>
<td>Nephrotoxic medications</td>
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* Iso-osmolar and low-osmolar contrast appear to reduce the risk of contrast nephropathy.

Table 1. Contrast-induced acute kidney injury (CI-AKI) risk according to glomerular filtration rate

<table>
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<tr>
<th>Glomerular filtration rate (mL/minute)</th>
<th>CI-AKI risk (%)</th>
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<tbody>
<tr>
<td>&gt;60</td>
<td>5.2</td>
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<tr>
<td>60-45</td>
<td>8.0</td>
</tr>
<tr>
<td>45-30</td>
<td>12.9</td>
</tr>
<tr>
<td>&lt;30</td>
<td>26.6</td>
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leading to increased risk of CI-AKI. Contrast osmolality plays an important role in the development of CI-AKI. High-osmolar contrast media (HOCM) allow a good vascular opacification, but are more often associated with allergic reactions, and have a higher rate of CIN as compared to low-osmolar contrast media (LOCM), especially in high risk patients.21 Since LOCM still have higher osmolality than blood (890mosmol/L vs. 290mosmol/L), the advent of iso-osmolar contrast media (IOCM; iso-osmolar compared to blood) was further promising, but a systematic review of 17 trials, with 1,365 high-risk patients, showed that the risk of CI-AKI was similar using IOCM and LOCM.22

The incidence of CI-AKI with iohexol (low-osmolar) is higher than with iopamidol (low-osmolar) and ioxithalamate (iso-osmolar), while there is no difference between the latter two agents. This shows that although osmolality might play a key role in kidney damage, other factors, such as viscosity and iconicity, are also involved. Increased plasma viscosity directly impairs blood flow to the renal medulla by vascular and tubular mechanisms, and it is believed that IOCM (which have higher viscosity than both LOCM and HOCM) do not reduce the incidence of CI-AKI compared to LOCM. Ionic agents are more related to allergic reactions. As described above, HOCM (which are always ionic) are more related to this complication. When ioxaglate (ionic LOCM) and ioxithalamate (non-ionic IOCM) were compared, hypersensitivity reactions occurred in 2.5% vs. 0.7% of patients (p=0.007).23

CLINICAL IMPLICATIONS

The most common manifestation of CI-AKI is an asymptomatic transient decline in renal function, which starts within 24 hours of procedure, has a peak in 3 to 5 days, and returns to baseline within 14 days. Approximately 1% of patients who develop CI-AKI may require hemodialysis due to oliguric renal failure, volume overload and hyperkalemia; of those, up to one fourth (0.23%) will require permanent dialysis or kidney transplantation.24

CI-AKI is associated with higher rates of access-site complications, including bleeding, hematoma and pseudoaneurysms.4 Non-cardiac complications, such as stroke, pulmonary embolism and gastrointestinal hemorrhage are also more common. The length of hospital stay in patients with CI-AKI is approximately 1.5 fold longer than in patients with no CI-AKI.25 Acute renal failure requiring dialysis after PCI is a particularly severe complication associated with in-hospital mortality rate of 27%.24 The in-hospital rate of myocardial infarction is approximately 4% in patients who develop CI-AKI, compared to 2% in patients who do not present such condition. The rates of myocardial infarction are even higher (7.9%) in patients who require dialysis.18

Both in-hospital and long-term mortality are higher in patients who develop CI-AKI (Figure 3). These findings are consistent throughout the literature, with follow-up periods as long as 5 years.4,14,8,26,27 However, since all data available are based in observational studies, researchers have recently questioned the true impact of CI-AKI in hard outcomes, suggesting that it is only a marker of high risk patients who developed clinical events despite of CI-AKI.25,28 Acute kidney injury is strongly associated with important risk factors for mortality, such as preexisting CKD, diabetes, left ventricular dysfunction and markers of more aggressive atherosclerosis (i.e. cerebrovascular disease). Moreover, it is curious to see how a transient decrease in glomerular filtration rate (GFR), with total recovery within a few days, can be associated with such an increase in mortality. On the other hand, it is possible that acute tubular injury triggers clinical events in other organs with mechanisms still not completely understood. Yet, it is of great importance trying to anticipate CI-AKI while this doubt remains unsolved. Defining the association of AKI with an adverse long-term prognosis identifies a high-risk cohort that warrants aggressive secondary prevention and monitoring.

TREATMENT

There is no specific treatment for CI-AKI. Thus, the main strategy to avoid it lies on prevention and identification of high-risk patients. Multiple prediction models have been created in different populations using discrepant CI-AKI definitions.11,15,29-32 Given the distinct clinical characteristics of each population, these models perform well where they were developed, but may not predict CI-AKI so effectively in different scenarios. Mehran risk score15 is the most commonly used predictive model, and includes eight variables (hypotension, intra-aortic balloon pump, congestive heart failure, chronic kidney disease, diabetes, age >75 years, anemia, and contrast volume) with a cumulative score dividing patients from low (7.5%) to very high risk (57.3%) of developing CI-AKI. When compared to another widely used risk model in a population from northwest
USA undergoing elective or urgent PCI, Mehran risk score was found to predict CI-AKI more accurately. When compared to ACEF-MDRD score in a population from southern Brazil undergoing primary PCI, Mehran risk score was less accurate.\(^\text{34}\) ACEF-MDRD score had an excellent negative predictive value (92.6%; 95% CI: 88.9-95.4%), and had the advantage of using only three variables to be calculated. Ideally, each population should have their own risk prediction tool.

The management principles include minimization of the total amount of contrast (i.e. biplane coronary angiography, "staged" procedures, avoid ventriculography) and routine use of hydration protocols before contrast exposure.\(^\text{35}\) Volume expansion inhibits the renin-angiotensin system, dilutes the contrast media, and protects against reactive oxygen species.\(^\text{36}\) Administration of iso- or low-osmolar rather than high-osmolar contrast media is also recommended,\(^\text{22}\) as well as avoiding use of concomitant nephrotoxic agents. Figure 4 shows a flowchart of suggested management of CI-AKI according to baseline risk factors.

Hydration is the cornerstone for prevention of CI-AKI, by increasing renal flow, reducing the contraction of renal vessels and diluting direct nephrotoxic agents. Only intravenous hydration with isotonic sodium chloride is uniformly accepted in clinical practice, with consistent evidence of its effectiveness in reducing CI-AKI.\(^\text{37-39}\) Although there is a recent article questioning the true impact of hydration in preventing CI-AKI,\(^\text{40}\) the patients in this study had very low risk of developing CI-AKI, and risk reduction could not be observed. In such patients, oral hydration is at least as effective as intravenous hydration.\(^\text{41}\)

Excessive hydration and volume overload, however, may be deleterious and increase CI-AKI risk,\(^\text{42}\) probably due to increased afterload, similar to what occurs in cardiorenal syndrome. In order to guarantee an euvolemic state, hemodynamic-guided hydration have been tested and proved to reduce CI-AKI incidence in patients with heart failure and/or chronic kidney disease. Central venous pressure\(^\text{43}\) and left ventricular end-diastolic pressure\(^\text{44}\) were the strategies used to guide hydration.

Sodium bicarbonate hydration is not more effective than sodium chloride volume expansion, but has the advantage of using less volume when volume overload is not desired (i.e. patients with heart failure). While sodium chloride protocols recommend an infusion of 1mL/kg body weight per hour, 12 hours before and 12 hours after administration of the contrast agent, a widely-used sodium bicarbonate protocol\(^\text{45}\) consists of 3mL/kg body weight for 1 hour before, and 1mL/kg during contrast exposure, and for 6 hours after the procedure. There are at least six meta-analyses\(^\text{46-50}\) comparing sodium bicarbonate and sodium chloride (among other strategies), showing conflicting results. The ones favoring sodium bicarbonate were performed in higher risk patients and with higher event rate. One of the studies\(^\text{48}\) showed a reduction in mortality with sodium bicarbonate (hazard ratio 0.61; 95% CI 0.41-0.89; p=0.011), although there was a statistically significant interaction between the effect on mortality and the occurrence of

![Figure 4](Image). Flowchart of suggested management of contrast-induced acute kidney injury, according to baseline risk factors. GFR: glomerular filtration rate.
CI-AKI. A recent randomized controlled trial including 4,993 high-risk patients did not show benefit of intravenous sodium bicarbonate over intravenous sodium chloride for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days.51

High volumes of crystalloid infusion with forced diuresis (RenalGuard system®) were compared with sodium bicarbonate, and were found to reduce the incidence of CI-AKI in high-risk patients submitted to PCI and transcatheter aortic valve replacement (TAVR).52,53 RenalGuard® measures and controls intravenous crystalloid volume with urine output, increasing the urine flow rate (>150mL/hour) and reducing the toxic effect of contrast medium. The device, however, is not widely available and its use has not been very popular.

Statins are the only pharmacological intervention to date that consistently prevents CI-AKI, probably through their pleiotropic effect on inflammatory pathways, endothelial reactivity, and apoptosis. Statins reduce the incidence of CI-AKI irrespective of the presence of diabetes and CKD.54 However, one can argue that while statins are known to reduce the incidence of other cardiovascular outcomes it can also consequently decrease the incidence of CI-AKI.

Other pharmacological therapies remain controversial. There have been small randomized trials showing benefit from agents, such as theophylline, trimetazidine and ascorbic acid, among others;55-59 however, because of the small benefit and the inconsistent results in larger randomized trials, there is currently no conclusive evidence to broadly use any of these medications. Acetylcysteine is an agent that consistently prevents CI-AKI, probably through the toxicity of contrast medium-induced declines in renal function at 90 days.51

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the incidence of CI-AKI and should be avoided.60 By reducing intraglomerular pressure due to efferent arteriolar dilation, they may cause loss of ability to raise intraglomerular pressure to maintain glomerular filtration and forward flow of urine through the proximal tubules and the remainder of the nephron.

CONCLUSION

Contrast-induced acute kidney injury is a common complication in patients receiving iodinated contrasts, and even more common in patients with ST-elevation myocardial infarction submitted to invasive cardiac interventions. The lack of effective treatment strategies once contrast-induced acute kidney injury develops, in conjunction with the demonstrated long-term risks associated with the development of contrast-induced acute kidney injury, make identification of high-risk patients and targeted implementation of contrast-induced acute kidney injury preventative strategies be the best contemporary approach to avoid harmful effects associated with contrast-induced acute kidney injury.


