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Epidemiology, Clinical Features and Diagnosis of Contrast Induced Nephropathy: A Brief Review

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Abstract

Contrast-Induced Nephropathy (CIN) is defined as acute deterioration of renal function after the administration of radio-contrast materials, mostly within a period of 24 to 48 hours. As we perform more contrast-containing procedures and imaging such as coronary angiography and angioplasty or computed tomography, it is expected that CIN will be increasingly common in our day-to-day practice. CIN is projected to account for 15% of episodes of acute kidney injury occurring in hospital. However, CIN carries a long-lasting adverse impact on patient outcomes rather than transient impairment of volume/electrolytes regulation only. The pathophysiological sequences behind include the tubulotoxicity of contrast per se, the induction of oxidative stress in the renal microenvironment, and the vasoactive properties of contrast materials. Although traditionally serum creatinine is utilized as means of diagnosing CIN, the emergence of new biomarkers and new classification schemes of AKI facilitate earlier diagnosis and planning of strategies to mitigate the influence of CIN. It is of paramount importance for physicians to be aware of the clinical features, courses and means of preventing CIN, so as to reduce the incidence of this potentially avoidable complication.

Keywords: Acute kidney injury; Contrast nephropathy; Radiocontrast

Introduction

Roughly 1.4 million of catheterization procedures are performed in U.S. each year, and more enhanced computed tomography is arranged for various purposes [1]. For these procedures, Contrast Medium (CM) is widely used with either diagnositc (coronary angiography) and therapeutic (coronary angioplasty) intent, and parenteral administration of iodinated CM is a common precipitator of Contrast-Induced Nephropathy (CIN) (or Contrast-Induced Acute Kidney Injury [CIAKI]) [2,3]. Expectedly more patients would develop CIN with the advancement of medicine, and currently CIN is already the third most common cause of hospital-acquired AKI in registry studies [4]. It is gradually recognized that development of CIN predicts elevated risk of late Acute Myocardial Infarction (AMI), longer in-hospital stay [5], and more complicated hospitalization course [6], and higher in-hospital mortality. Patients with CIN also have significantly higher in-hospital mortality (7-22%) as well as 1-year (12-37%) and even 5-year mortality (44-78%) than those without CIN [2,7-9]. More importantly, contrast induced AKI correlates with higher healthcare resource utilization including hospitalization cost [10], especially if such CIN episode is dialysis-requiring. As our knowledge of the pathogenesis and the risk factors of CIN expands, these progresses assist significantly in devising strategies to prevent CIN after CM injection. Consequently, a thorough understanding of the epidemiology, pathophysiology, clinical manifestations, diagnosis, prevention strategy and management of contrast-induced AKI is critical for Gen Med (Los Angel) ical practitioners.

Epidemiology

The incidence of CIN varies widely among the existing literature, ranging from 5% to 25% after CM injection, according to clinical settings and definitions chosen [2,11-13]. In patients with Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD), the average incidence is reportedly 9-11% [11,12]. The definition of CIN has to consider 2 main components; the time frame required for renal function biomarkers change, and the magnitude of biomarkers change. CIN is typically coded according to an increase in Serum Creatinine (sCr) within the first 24 or 48 hours after contrast injection [2,12]. However, others have proposed that a 24-hour interval best captures the group of patients who "really" develop CIN. Still others claim that, for clinical dignosis of CIN, it should take at least 48-hour for confirmatory exclusion [14]. The European Society of Urogenital Radiology (ESUR) has produced guidelines on CIN since 1999, and subsequently revise them in 2011 [15,16]. According to these guidelines, CIN is arbitrarily defined as "a condition in which an impairment in renal function (increase in sCr by more than 25% from baseline level, or at least 0.5 mg/dL) occurs within 72-hour following intravascular administration of CM. Alternative etiologies of sCre change should be excluded [15].

Recently, the threshold for diagnosis of AKI has been debated, since accumulating evidence suggests that minimal sCr change could be associated with significantly worse outcomes [17]. For these reasons, in 2007, Acute Kidney Injury Network (AKIN) group proposed a extended classification scheme for staging AKI, with mild AKI (stage I) defined by an elevation of sCr 0.3 mg/dL within 48 hours [18]. This evolution enhances the diagnostic sensitiviy of CIN. However, concerns have been aroused against this definition, for being over-sensitive and increasing false positive rates [19]. Nonetheless, most researchers now opt to diagnose AKI and also, CIN, with a lower threshold of sCr within a predefined period, to facilitate earlier recognition.

Risk factors

Risk factors identification is very important for clinicans to reduce the incidence of diseases. Similarly, identification of susceptible populations to CIN before CM exposure is important, since proper patient preparation, indications and CM adminstration route classification can effectively lower the risk of CIN [4]. Currently, risk

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Patient level	Procedure level
Ageing	Contrast medium volumes
Diabetes mellitus	Contrast medium osmolality
Pre-existing renal insufficiency	Route of administration
Arterial hypotension	Medications
Absolute intravascular volume depletion status	
Relative intravascular volume depletion status	

Abbreviations: CIN; Contrast-induced nephropathy

Table 1: Factors associated with increased risk of CIN.

factors for CIN development can be separated into 3 parts: patient level, medication, and procedure level factors.

Patient Level Risk Factors (Table 1)

Ageing

Advanced age is an important factor that enhances the probability of developing CIN. The definition of advanced age differs between studies, but generally a cut-off range of 65-75 years is agreed upon [13]. Being older than 75 years can carry a 2-5 fold higher risk of CIN, and it is estimated that every one-year increment after 75 years predicts a 2% increased risk [6,13,20]. Aging per se denotes the physiologic degeneration of renal structure, function, and also the recovery ability after various nephrotoxic insults [21,22]. Most experts concur that a baseline renal function should be measured in elderly patients before exposure to CM [2,16].

Diabetes Mellitus (DM)

DM has been established as an independent risk factor for CIN. Presence of DM is associated with a 1.5 ~ 3 fold higher risk of AKI after CM exposure. Furthermore, DM amplifies the risk conferred by pre-existing renal insufficiency alone [11,13,20]. The mechanisms include a predisposition of the host kidney to ischemic injury (from vasculopathy), increased oxidative stress/free radical damage, and endothelial dysfunction [23]. Fluid retention in DM patients also increases the use of diuretics, also a risk factor for CIN [24]. Likewise, a pre-procedural glucemic level higher than 200 mg/dL is also a risk factor for CIN [25].

Pre-existing renal insufficiency

This is probably the most important risk factor for CIN. Most studies showed that a baseline renal insufficiency independently predicts higher risk of CIN episodes [5,6,8,11,13,20], and the risk is directly proportional to the baseline sCr values [6,13]. Rihal et al. identified that patients with pre-procedural sCr 1.2-1.9, 2.0-2.9, >3 mg/dL, had a graded increment in the risk of subsequent CIN (odds ratio [OR] 2.4, 7.4 and 12.8, respectively) [20]. One-third of patients with sCr higher than 2.0 mg/dL and receiving CM will ultimately develop CIN [26,27].

It should be noted that the definitions of renal insufficiency vary widely between studies. Most researchers now use the Kidney Disease Outcome Quality Initiative (KDOQI) CKD staging in their studies, for which glomerular filtration rates (GFR) are utilized for classification [16]. Renal insufficiency, or CKD, is usually defined as a baseline GFR lower than 60 ml/min/1.73 m^2 (CKD stage 3 or higher) based on the KDOQI scheme, but there are criticisms concerning this issue [28]. Nonetheless, sCr-based estimation of GFR is currently still the most prevalent means of grading patients' baseline renal function. Patients with estimated GFR higher than 60 ml/min/1.73 m^2 should be regarded without renal insufficiency when we evaluate the risk of CIN for patients with CM

exposure, unless they have other evidence of renal diseases [29].

Arterial hypotension

Hemodynamic instability has been quoted as a risk factor for CIN, manifesting in covariates such as hypotension. The mechanisms presumably involve renal hypoperfusion with resultant renal ischemia [2,27]. Placement of Intra-Aortic Balloon Pump (IABP) could also raise the risk of CIN, through potential arterial hypotension, intra-operative factors (complicated and longer procedures) and post-operative complications (atheroemboli detachment) [5,11,13]. Gruberg et al. discovered that use of IABP doubles the risk of CIN in catheterized patients [30]. Furthermore, anemia can also be regarded as a surrogate with similar mechanisms predisposing to CIN (reduction of tissue oxygenation) [31].

Absolute/Relative Intravascular Volume Depletion

Dehydration is often touted as a risk factor for CIN, but few studies actually prove this link [20,32,33]. Illnesses such as congestive heart failure (CHF) also potentiate the development of CIN through mechanisms akin to dehydration [2,13]. Many cohort studies have shown that CHF (with a New York Heart Association [NYHA] grade 3-4 severity) is associated with 50% higher risk of CIN [11,13,20]. There are also studies showing that AMI within 24 hours of PCI with a low Left Ventricular Ejection Fraction (LVEF) independently predict occurrence of CIN [5,20]. The mechanisms include elevating oxidative stress, increasing renal vasoconstriction as well as oxygen consumption levels from rising renal sodium reabsorption [34].

Medication factors

Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs), through their glomerular hemodynamic effect, have been implicated in predisposing patients to CIN, but very few studies prove this causality [27]. Umruddin et al. ever demonstrated that ACEI or ARB use is associated with 3-fold higher risk of developing CIN after coronary angiography [35]. Withdrawal of ACEI or ARB before coronary procedures did not seem to reduce the risk of subsequent CIN [36]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are one other class of medications renowned for their adverse impact on risk of developing CIN [37]. Through the interruption of intrarenal prostaglandin production, NSAIDs impede the renal autoregulatory actions during nephrotoxic insult, and intuitively should elevate risk of CIN. However, a small study identified no obvious increase in risk of CIN in NSAID users [38]. Further study is still warranted to prove this association.

Other agents such as cyclosporin, tacrolimus, platinum-based chemotherapeutic regimens and aminoglycosides can all be culprits in CIN, but little data exists for such association [39]. Nonetheless, physicians a are still advised to refrain from these medications, if possible, in patients preparing for CM exposure. In addition, use of metformin in CIN patients could raise the risk of subsequent lactic acidosis, and discontinuation of metformin should be considered in this setting.

Procedure-related risk factors

Osmolality of CM: Iodinated CM are structurally composed of carbon-based skeletons and iodine atoms, rendering the molecules radiopaque. CM are classified according to their osmolality into 3 types: high-osmolal (HOCM) (ex. diatrizoate; osmolality ~2000 mOsm/kg); low-osmolal (LOCM) (ex. Iohexol, iopamidol, ioxaglate; osmolality 600~800 mOsm/kg), and isosmolal (IOCM) (ex. iodixanol;

osmolality 300~400 mOsm/kg) [2]. Earlier meta-analysis before 1990 demonstrated that the risk of CIN decreased substantially after the introduction of LOCM [40]. HOCM is now an established risk factor for CIN [2,7,12,16]. Different IOCM agents do not seem to display clinically different effect, with IOCM class possessing the lowest risk of CIN [41-44].

Volume of CM: The volume of administered CM can be another important risk factor for CIN. Mean contrast volume is found to be an independent predictor of CIN, and even small volumes of CM (~30 ml) might trigger renal injury in high-risk patients [8,13,44-46]. For every 100 ml increase of CM used, there is a concomitant 12% increase of the risk [20]. Several groups proposed that the volume of contrast administered should not exceed twice the number of a given patient's baseline eGFR value (in mililiter) [2,47].

Route of CM administration: Circumstantial evidence has pointed out that intra-arterial injection of contrast medium carries a higher risk of contrast-induced AKI than intravenous use [13,48]. No mechanisms have been provided currently [2]. Some speculations, including the lower dose of CM in intravenous route (than arteriography), less hemodynamically unstability, risk of atheroembolism in arterial studies, have been proposed [2,16]. Thus, if both indications exist with equal risk-benefit ratio, a choice of intravenous administration of contrast medium might be better.

Clinical Course

The norm of CIN is that sCr begins to rise within 24 hours after contrast medium administration, peaks at 3-5 days, and returns to baseline level or near baseline within 1-3 weeks [49]. Most patients developing CIN do not require dialysis, but they do have poorer short-term and long-term survival [8,30]. Gruberg et al. reported that only 0.4% of patients require hemodialysis after CIN occurred, but those necessitating dialytic support had particularly higher mortality (12-35%) [27,30].

Pathophysiology

The pathophysiologic sequence of CIN involves two components: vasoactive mediator-related vasoconstriction with resultant renal ischemia; and the direct tubulotoxicity exerted by CM [27].

First, CM are capable of altering renal hemodynamics through their actions on renal vasoactive agents [27]. The high osmolality of CM could induce renal blood flow decrease, and CM per se also enhance erythrocyte aggregation [50,51]. In addition, CM have also been reported to cause shunting of blood flow to the renal cortex, leading to medullary ischemia and tubular necrosis [52].

Second, CM are also tubulotoxic. The tubulotoxicity of CM manifests as epithelial vacuolization, cellular necrosis or apoptosis and interstitial inflammation [53]. Antioxidant enzymes are reduced during experimental CM exposure for rat kidney [27]. The higher osmolality of CM can also contribute to its tubular toxicity through solute diuresis and subsequent tubuloglomerular feedback activation, with GFR reduction [27]. Consequently, the mechanisms of direct CM tubulotoxicity involve not only the induction of oxidative stress, but also the inherent hyperosmolality.

Risk Prediction and Modeling

Many research groups have strived to develop predictive models for patients with high risk of developing CIN. Mehran et al. developed a simple scoring method that integrates 8 baseline clinical variables

to evaluate the risk of CIN after coronary angiography, including age (>75), hypotension, CHF, anemia, DM, CKD (sCr>1.5 mg/dL), use of IABP, and volume of CM [13]. They found that the incidence of CIN ranged from 7.5% in the low risk category, to 57.3% in the very high risk category. Bartholomew et al., in another large cohort of CIN patients, derived a risk scoring scheme composed of DM, CHF, hypertension, peripheral vascular disease, IABP use, CKD (creatinine clearance <60 ml/min/1.73 m^2), and contrast volume ($\geq$ 260 ml) [11]. Incidence of CIN ranged from 0.5% in the lowest risk category, to 43% in the highest risk category. These studies proved that the risk factors outlined above are mutually additive, and risk of CIN increase prominently as risk factors accumulate. However, none of the reported studies have been prospectively applied, and the utility in real-world is still in question. It is currently still premature to recommend the routine use of these models in risk stratification of specific population [2].

Diagnosis – New Biomarkers

Other rapidly-responsive serum markers aiming at earlier detection of renal function change also are under investigation. Cystatin C is a cationic low molecular weight cysteine protease, freely filtered by glomeruli, thus serving as a good marker for assessing Glomerular Filtration Rate (GFR) [54,55]. A japanese study found that serum cystatin C measurement after angiography significantly correlates with AKI development [56,57]. Cystatin C is particularly useful in patients with diabetic history.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a small stress protein released from injured tubular cells after various stimuli [58]. Multiple studies have documented excellent sensitivity and fair specificity in earlier detection of AKI [59-61]. Hirsch et al. first demonstrated that urinary NGAL predicts contrast-induced AKI fairly with 73% sensitivity and 100% specificity, while others also reach similar conclusions [62,63].

Other potential biomarkers for contrast-induced AKI, include kidney-injury molecules -1 (KIM-1) and urinary L Type Fatty Acid-Binding Protein (L-FABP), but few human studies are available at this time [64,65]. Nonetheless, a close monitoring of sCr change and other markers of renal function change after contrast exposure is still crucial and necessary to detect any evidence of contrast-induced nephropathy after PCI.

Conclusion

Contrast-induced AKI, or contrast-induced nephropathy, is a growing issue in the contemporary field of intervention cardiology and also in fields like diagnostic radiology. Although the definitions of contrast-induced AKI are still changing with the advancement of new biomarkers, the most cost-effective method is still serum creatinine in light of the economic burden encountered in most countries. As the understanding of the pathogenesis of CIN also progresses, more and more strategies for prevention of contrast-induced AKI will be developed and tested clinically. It will be vital for primary care physicians and cardiologist to carefully choose their patients for contrast medium containing procedure and stratify the risk of these patients, to reduce this potentially avoidable complication.

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