

# Delayed Recovery of Contrast Induced Kidney Injury Post Angiography: Rate and Risk Factors

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## Abstract:

**Background:** Exposure to Contrast media is the third leading cause of hospital acquired acute kidney injury. It follows a predictable time of onset and a less predictable scenario in recovery. This is related to certain factors, but at the end there will be a substantial association with increased mortality, morbidity, and length of hospitalization.

**Objectives:** To define the Incidence of persistent contrast induced renal impairment a month after angiography and to define the risk factors for such persistence

**Patients and Methods:** One hundred and one patients (101) were enrolled in this study. All were referred to the Iraqi Center for Heart Diseases in Baghdad/ Iraq for coronary and/or peripheral vascular angiography from October 2009 to July 2010. All patients' clinical and laboratory data including baseline renal function tests were ordered and recorded with subsequent risk categorization. Post procedure serum creatinine checked on regular intervals (48 hours, one week, and then weekly for three months for those with serum creatinine consistent with the contrast induced - acute kidney injury (CI-AKI) definition at 48 hours.

**Results:** The mean age for the study group was 62±16.9 with 78 (77%) male. Twenty three patients (22.7%) had diabetes mellitus. Thirteen patients (12.7%) had a pre-existing renal impairment. Twenty one patients (20.7%) received extradoses of contrast. Thirty two patients (31.6%) developed CIN by the definition within 48 hours of the procedure with the mean serum creatinine of 1.8 mg/dl. Seven patients (6.8%) continued to have impaired renal function at week 4 and persisted to have such low GFR up to three months of the procedure. Baseline low GFR, Diabetes mellitus and extradoses of contrast were independent risk factors for the occurrence of CIN and delayed renal recovery.

**Conclusion:** The risk of poor renal recovery after contrast cannot be overlooked. Preexisting renal function impairment, diabetes mellitus, and extra doses of contrast media are independent risk factors for such delay.

**Key Words:** Contrast media, Nephrotoxicity, AKI, Angiography.

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## Introduction:

Contrast-induced nephropathy (CIN) is the third most common cause of hospital acquired renal failure, after decreased renal perfusion and nephrotoxic medications.<sup>1</sup> It is usually defined as an impairment of the renal function occurring within 48 hours after the administration of contrast media. It is manifested as an absolute increase in serum creatinine (Scr) level by at least 44 mmol, or by relative increase of at least 25% over the base line value after excluding other causes of renal function deterioration. It should be recognized that in minority of cases, the peak increase of SCr may occur up to 5 days after contrast exposure.<sup>2</sup> It is not surprising that the reported incidence of contrast induced- acute kidney injury (CI-AKI) varies widely across the literatures, depending on the definitions used, the

patient population, and the baseline risk factors.<sup>3</sup> Depending on the threshold criterion for CI- AKI chosen, this variation can lead to rates of 6–35%. It is accepted that, in patients with normal renal function - even in the presence of diabetes-the risk for CI-AKI is low (1–2%). However, the incidence may be as high as 25% in patients with pre-existing renal impairment or in presence of certain risk factors, such as the combination of CKD and diabetes, CHF, advanced age, and concurrent administration of nephrotoxic drugs.<sup>4,5</sup> The pathogenesis of CIN is not clear. Studies in vitro and in animals suggest that CIN is due to a combination of toxic and ischemic injury to the renal tubular cells. Proximal and distal tubular injury occurs at the moment of contact with contrast medium and is thought to be due to interplay of intra-renal vasoconstriction, medullary hypoxia, and direct tubular cell death.<sup>6,7</sup> Baseline kidney function strongly determines the risk of CIN, and the degree of Kidney impairment at baseline correlates with a proportionate risk for CIN. Diabetes, increased age, higher dose of contrast agent used, route of contrast administration (intra-arterial vs

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intravenous), congestive heart failure (CHF), hypertension, peri-procedural shock, baseline anemia, post procedural drop in hematocrit, use of nephrotoxins, and nonsteroidal anti-inflammatory medications, volume depletion, increased CKMB, and need for cardiac surgery after contrast exposure, have been associated with increased risk of CIN. Mehran et al devised an algorithm for risk prediction of CIN and the need for dialysis in a general population of patients who underwent coronary angiography, and subsequently validated the prediction score in a separate cohort of patients, 26% of whom had CKD (estimated glomerular filtration rate [eGFR] <60 mL/min).<sup>8,9</sup> Searching pub med yielded little about the concept of delayed renal recovery but some studies looked for mortality, long term adverse events like ESRD. Regardless of the definition of CIN and after adjustment of baseline risk factors, adverse events like ESRD was twice high in those developed CIN after exposure.<sup>10</sup> Patients who develop CIN have been shown to have a higher rate of in-hospital mortality, diminished long-term survival when compared with those who do not.<sup>11,12</sup> The trial reported by Sadeghi et al. found that the relative risk of 1-year mortality of 7.4 for those who developed CIN compared with those who did not.<sup>13</sup> In patients with pre-existing CKD, the impact on survival is particularly more negative.<sup>14</sup> In a study by Wi J et al Mehran risk score predicted CIN with persistent renal dysfunction and long-term clinical outcomes in patients with AMI.<sup>15</sup>

**Aim of the study :** to study the rate of delay in renal recovery a month of exposure to contrast media in angiographic studies, and to identify the risk factors for such delay, this study was conducted.

#### Patients and Methods:

A single center prospective study recruited one hundred and one patients who had been referred to the Iraqi Center for Heart Diseases in Baghdad/ Iraq from October 2006 to July 2007 for coronary or peripheral diagnostic and/or interventional angiography. After having their formal acceptance to be enrolled in this study, all patients had been interviewed, clinically examined and sending for routine laboratory investigations. The aims were to search for the presence of any recognized risk factors for CIN. Baseline renal function was assessed by measuring blood urea nitrogen (BUN) and serum creatinine (S. Cr). Four variables MDRD equation was used for calculating eGFR as follows;  $eGFR = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{0.203} \times [1.210 \text{ if Black}] \times [0.742 \text{ if Female}]$ , Serum Creatinine is in mg/dl. A peri-procedural hydration with intravenous administration of 0.9% isotonic saline administered in a dose of 1-3 ml/kg/min for 6-12 hours according to patients volume status. All nephrotoxic medications had been omitted. Any patients with diabetes mellitus who was already on metformin advised to stop it and insulin therapy was introduced instead. ACEIs and diuretics were switched to other anti-hypertensive medications prior to the procedure. The patients risk category

identified according to CI-AKI risk-scoring model for percutaneous coronary intervention by Mehran et al.<sup>9</sup>, Table(1)

**Table(1): CI-AKI risk-scoring model for percutaneous coronary intervention by Mehran et al**

Risk factors	Integer score (calculate)
Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast-media volume	1 per 100 ml
SCr > 1.5 mg/dl (> 132.6 μmol/l)	4
or	
eGFR <60 ml/min per 1.73 m <sup>2</sup>	2 for 40-60
	4 for 20-39
	6 for <20

Low risk: cumulative score <5; high risk: cumulative score >16. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. Development and initial validation. *J Am Coll Cardiol.* 2004; 44:1393-1399.

In all procedures, iohexol (Omnipaque®) which is a water soluble low-osmolar contrast media has been used. A contrast volume of 3-5/kg body weight used and any volume larger regarded as an extra dose. Post procedure serum creatinine level had been checked on regular intervals; at 48 hours and on the seventh day. For those who fulfill the CNI-AKI definition criteria, renal function tests were followed by repeated measurements of Scr level on weekly bases for three months. A rise in S. Cr level of greater than 25 percent above the baseline or an absolute rise of greater than 0.5 mg/dl considered abnormal. We didn't study the effect of pharmacological and non pharmacological interventions to prevent or to treat CIN-AKI.

#### Statistical analysis:

Data were tabulated and arranged by using (SPSS 14), NO, % and mean ±SD used to summarize data. Multivariate analysis was used to differentiate between independent and dependent factors. Association between variables were measured by chi-square test, difference between variables measured by t-test and ANOVA test P value < 0.05 considered significant.

#### Results:

The mean age for the study group was 62±16.9. Males were the predominant gender in the study 78 (77%), while females were only 23 (22.5%). Twenty three patients (22.7%) were having diabetes mellitus. Only 13 patients (12.7%) were having pre-

existing renal impairment. Their mean baseline eGFR was 41 ml/min.

Ten patients (9.9%) were high risk according to Mehran risk score. The contrast volume ranged from 50 to 500ml with mean of 301 ± 145.34 ml. Thirty two patients (31.6%) developed CIN by the definition within 48 hours of the procedure with the mean serum creatinine of 1.8 mg/dl. The number of patients who developed renal impairment at weeks 1,2,3, and 4 were 23 (22.8%), 17 (16.8%), 13(12.8%), and 7(6.8%) respectively. Those seven with persistently elevated serum creatinine at week 4 continued to have such impaired renal function up to three months of follow up. Twenty one patients (20.7%) received extradoses of contrast. Factors that significantly associated with CIN were diabetes mellitus (17/73.9%, p value < 0.001), preexisting renal impairment (13/100%,p value <0.0001), contrast volume (16/84.2%, p value <0.0001). Other factors with significant associations are hypertension (19/65.8%, p value <0.001), age (p value <0.025), and myocardial infarction (12/64.7%, p value <0.05). Multivariate analysis model identified that pre existing renal impairment (p value <0.0001), extra dose of contrast (p value <0.0001), DM (p value <0.001) , and (hypertension p value <0.003) were independent risk factors for the development and delayed recovery of Contrast induced AKI.

All seven patients who persistently had elevated serum creatinine at one month were diabetics, with baseline renal

impairment and received extradoses of contrast (100%). Table(2) shows the baseline characteristics of the study group.

**Table (2) The Baseline Characteristics of the study group**

Variables	Numbers %
<b>Gender</b>	
Male	78 (77.7)
Female	23 (22.3)
<b>Age ( yr)</b>	19-75 (62±16.9)
<b>BMI</b>	19-25 (22.6±1)
<b>Pre-existing renal status</b>	13 (12.7)
DM	23 (22.7)
HT	30 (29.7)
MI	32 (31.7)
<b>Heart failures</b>	27 (26.7)
<b>Shock/ IABP</b>	2 (1.8)
<b>IABP</b>	1
<b>Contrast volume/ml</b>	50-700

Table(3) discloses the distribution of the study group according to the independent risk factors by multivariate analysis.

**Table (3) Distribution of the study group according to the independent risk factors by multivariate analysis.**

Risk factors	Pre test	Week 1	Week 2	Week 3	Week 4	3 months	P – value
<b>Preexisting renal Impairment</b>	13(12.9)	13(100.0)	11(84.0)	9(81.8)	7(77.8)	3(42.0)	0.0001
<b>Diabetes Mellitus</b>	23(22.5)	17(73.9)	13(68.4)	8(61.5)	6(60.0)	4(66.7)	0.001
<b>Hypertension</b>	30(29.7)	20(66.7)	17(85.0)	12(70.6)	9(75.0)	6(66.7)	0.0001
<b>Extra doses of contrast in ml</b>		16(76.2)	14(87.5)	10(76.9)	5(55.6)	5(100.0)	0.0001

**Discussion:**

Contrast-induced nephropathy (CIN) is a common, serious problem in the interventional cardiology practice that is associated with increased morbidity, mortality, and healthcare cost. This study is consistent with the international data of the incidence and risk factors of CIN. Here it's imperative to say that angiography in this study was for diagnostic and interventional purposes and for coronary and peripheral circulations. This is just to clarify the heterogeneous nature of the study sample and this probably had its impact on result in some way. There is no consensus on the definition of CIN used by the society of urogenital radiology and this add to the difficulty in designing studies on the incidence of CIN and Contrast associated AKI and this can explain the wide variation of incidence from 6% to 35% in many data. This is probably related to the cut off percentage of increment in serum creatinine or to the time of measurement( 48 hour vs. 72 hours or later ). Even the rate

of day to day variation of serum creatinine in hospitalized patients has its effect on such definition and detection of CIN. In addition the background fluctuation of kidney function in patients receiving iodinated contrast has its impact on this definition. <sup>17,18</sup>Validated risk-prediction models using patient and procedural risk factors to assess for CI-AKI have been developed for patients undergoing percutaneous coronary intervention like the Mehran risk model. The overall occurrence of CI-AKI in the development set of the score was 13.1% (range 7.5% to 57.3 %for a low [<5] and high [>16] risk score, respectively); the rate of CI-AKI increased exponentially with increasing risk score. <sup>9,19</sup>Diabetes Mellitus DM (has significant effects on renal function after exposure to contrast media and this is consistent with the result of Parfery and Griffiths with a conclusion that even with normal renal function there is a little risk of clinically important nephrotoxicity attributable to contrast.<sup>20</sup> Pre-existing renal impairment is a strong predictor

for post catheterization renal impairment and there was strong association between pre-existence renal impairment and renal status one week after percutaneous coronary. This was consistent with the data from Rihal and Textor in their study.<sup>21,22</sup> Moore et al. found a highly significant relationship ( $p < 0.001$ ) between an increasing baseline level of serum creatinine and the frequency of nephrotoxicity (varying from 2% in those with baseline creatinine of  $< 1.5$  mg/dL to 20% in those with levels of  $> 2.5$  mg/dL).<sup>23</sup> In this study hypertension had a significant effects on renal function and this is similar to that found by Mehran and Nikolsky et-al, 2004. The duration of HT had no significant effects ( $p$  value  $< 0.005$ ) on the incidence while the effect of antihypertensive medications not studied with the predefined withdrawal of ACEIs and diuretics although their use may be of no effect according to some data like that of Goldenberg in 2005.<sup>9</sup>

In our study there was two patients with a systolic blood pressure of less than 100 mm hg ,one presented acutely with cardiogenic shock and the other was on IABP. Both developed CIN and AKI. It's well known that hypotension and hypovolemia will augment the injurious effect of contrast on renal tubules but it is difficult to extrapolate data because of small sample. <sup>9</sup> The volume of contrast was significantly associated with the risk of CIN .This was in accordance with the study of Mehran and colleagues. In this study the dose was based according to the worldwide standard practice of using contrast by 3-5 ml/kg body weight although the best practice is to base the dose according to the renal function which can minimize contrast dose in patients with renal dysfunction and the resulting planned contrast volume restricted to less than thrice and preferably twice the calculated creatinine clearance CCC might be valuable in reducing the risk of CIN. In another study a contrast media volume (CMV)/eGFR ratio  $> 5.35$  was a significant and independent predictor of CIN in patients with CKD.<sup>9,24,25</sup> CI-AKI is associated with an increased risk of mortality, cardiovascular events, renal failure, and prolonged hospitalization. However, the association between CI-AKI and mortality is strongly confounded by baseline clinical characteristics that simultaneously predispose to both kidney injury, delayed recovery, future risk of CKD/ESRD and mortality. The main baseline characteristics that confound such risk are diabetes mellitus and a preexisting impaired renal function as in this study.<sup>26</sup> Despite all the standard prevention protocols seven patients developed and continued to have impaired renal function at one month after the procedure and all of them had coexistence of all these three risk factors.

#### Conclusion:

In conclusion, the risk of delayed renal recovery after contrast cannot be overlooked. Better attention on renal based contrast dose is mandatory. Larger longitudinal studies with ESRD risk

and survival as the main outcome in relation to the risk factors will be certainly helpful.

#### Authors contributions:

Hilal Al-Saffar: The supervisor; Design the study, discusses results, and contribute in writing the manuscript.

Adel J Yassin: Design the study, collect the sample, calculate the results and write the draft of the manuscript.

Ala Ali: Revise the design of the study, critically review the draft of the manuscript, and discuss the renal part of the study.

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