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## FULL PAPER

# The role of inflammation in contrast-induced nephropathy

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**Objective:** Global incidence of contrast-induced nephropathy (CIN) is 2–5%, but a recent Kenyan study highlighted a local incidence of 12–14% without offering an explanation for the higher incidence. This study proposes that inflammatory states confer a higher relative risk for development of CIN. Our objective was to determine the risk of developing CIN given the presence of an inflammatory state in patients in Kenya.

**Methods:** Prospective cohort study of patients undergoing a contrast-enhanced CT (CECT) scan in a private university teaching hospital in Kenya and having no known risk factors for CIN. 423 patients were recruited and grouped into those without inflammation (unexposed) having serum C-reactive protein (CRP) levels  $\leq 5 \text{ mg dl}^{-1}$  and those with evidence of inflammation having CRP levels  $> 5 \text{ mg dl}^{-1}$ . Serum creatinine (SCr) was measured

before the CECT and 48 h following the CECT with CIN diagnosed by an increase of  $> 25\%$  in the SCr from the baseline. Relative risk was determined and multiple logistic regression analysis performed on biophysical variables and contrast volume to assess their effect on development of CIN.

**Results:** Patients with high CRP levels had a relative risk of developing CIN of 2.16 compared with those with normal levels of CRP ( $p = 0.016$ ). No statistically significant association was seen between biophysical variables or volume of contrast and development of CIN.

**Conclusion:** Ongoing inflammation doubles the likelihood of development of CIN.

**Advances in knowledge:** This study highlights the importance of inflammation as a risk factor in the development of CIN.

Intravascularly administered iodinated contrast media are widely and liberally used in daily diagnostic radiological investigations. The reason for this is that with regard to volume administered, they are the safest intravascular pharmaceutical agents. They are invaluable in discernment of various pathological processes by radiologists through improved tissue contrast, thus enabling prompt diagnoses and management without performing invasive procedures. However, iodinated contrast media are not without side effects. Of these, few have received as much attention as contrast-induced nephropathy (CIN).<sup>1</sup> CIN is the third commonest cause of hospital-acquired renal injury, after hypotension and use of nephrotoxic drugs.<sup>2</sup>

CIN is defined as an elevation of serum creatinine (SCr) of 25% above the baseline within 24–72 h of administration of intravascular iodinated contrast media with no other identifiable cause of renal insult.<sup>3,4</sup> Because the majority of patients do not have follow-up measurement of SCr, a large number of patients who develop CIN pass unnoticed. Only 0.15–12.00% of patients who develop CIN require medical intervention for the condition.<sup>5</sup> This is a small subset of patients considering studies in general populations have revealed CIN incidence rates of 2–5%.<sup>6,7</sup> However, even in

subclinical CIN, Levy et al<sup>8</sup> demonstrated an excessive increase in all-cause mortality in patients who developed CIN, despite correction for other factors leading to mortality.

CIN is an iatrogenic insult to the kidneys caused by intravascular administration of iodinated contrast media. There is resultant kidney injury owing to multiple factors.<sup>9</sup> One of the effects of intravascular iodinated contrast media is transient vasodilatation followed by prolonged vasoconstriction.<sup>10,11</sup> An important hormone in this process is adenosine, which causes vasodilatation by alpha-2 receptor stimulation of the efferent arteriole and vasoconstriction via alpha-1 receptor stimulation.<sup>12</sup>

Vasoconstriction is the predominant effect.<sup>13</sup> While this occurs in all patients who receive intravenous iodinated contrast, the incidence of CIN in the general population infers that vasoconstriction alone is not a significant factor in CIN.

The other two main pathways that are implicated in the development of CIN are direct cellular toxicity and elevated urinary viscosity with resultant crystal stone formation and subsequent outflow obstruction.<sup>14</sup>

In an attempt to elucidate the cause of the elevated incidence of CIN, it was noted that other factors along with vasoconstriction may raise the risk of CIN.<sup>15</sup>

Low-income countries continue to grapple with a high infectious disease burden, which means that the population has a higher prevalence of inflammation than in high-income countries.<sup>16</sup>

It is well known that inflammatory mediators are thrombogenic.<sup>17</sup> Interleukins (ILs) are released in both infectious and malignant states, and IL-6 and IL-12 have been implicated in altering the haemostatic mechanisms in primates and humans.<sup>18</sup> IL-6 is known to induce acute phase reactant production, notably C-reactive protein (CRP).<sup>19,20</sup> Severe inflammatory states such as sepsis have been documented to increase the risk of developing CIN.<sup>17</sup>

Thus, if vasoconstriction is coupled with a prothrombotic state—defined as inflammation for the purposes of this study—it is possible that this would reduce renal perfusion and cause renal insult. Of note, the presence of acute inflammation has not been assessed as an independent variable affecting the development of CIN.<sup>21</sup>

CRP is a widely used biochemical marker for acute inflammation. It rises above normal limits within 6 h of onset of inflammation, peaks in 48 h and has a steady half-life that causes a rapid and predictable fall once the inflammation has stopped.<sup>22</sup> It thus presents a useful tool in objectively stratifying study populations into patients with and those without an active inflammatory process.

The majority of CIN studies are predominantly targeted at high-risk groups. Few of the studies look at the overtly normal population, and none of the studies has an incidence of CIN as high as 12–14% in the overtly normal population.<sup>23,24</sup>

An unpublished study by Mwanzi across three Kenyan hospitals demonstrated a CIN incidence of 12–14% [Mwanzi, Aga Khan University Hospital, 2009, personal communication], while showing that human immunodeficiency virus infection does not significantly influence the development of CIN.<sup>25</sup> The study did not, however, address the reason for this disproportionately higher incidence than the 2–5% found in other studies. This study therefore sought to identify factors that may be more predominant in the Kenyan setting that would significantly raise the incidence of CIN in the Kenyan populace.

## METHODS AND MATERIALS

A prospective cohort study in a private, tertiary teaching and referral hospital in Kenya enrolled a total of 423 consecutive patients who were undergoing a contrast-enhanced CT (CECT), gave informed, written consent and fulfilled the eligibility criteria detailed below.

The sole intravenous contrast medium administered in this study was non-ionic iso-osmolar 350 mg ml<sup>-1</sup> iodinated intravascular contrast medium. Patients received 50, 100 and 150 ml (17.5, 35.0 and 52.5 g) of iodinated intravenous contrast for CECT of the head, CECT of the chest/abdomen and CT angiography studies, respectively. These are the standard volumes of iodinated intravenous contrast administered for the above-named investigations in our department.

The patients were divided into two cohorts: the exposed group who had a CRP level of >5 mg dl<sup>-1</sup> and were thus considered to have a current inflammatory state and the unexposed group who had a CRP level of ≤5 mg dl<sup>-1</sup> (normal value) and were thus considered to not have a current inflammatory state.

## Eligibility criteria

All patients above the age of 18 years presenting to the university hospital who were to undergo a CECT scan within the study period were offered the opportunity to participate in the study. Patients were excluded from the study if any of the following features were noted: known risk factors for CIN that include pre-existing impairment of renal function (SCr >120 μmol l<sup>-1</sup>); patients who had recently (<3 months) used nephrotoxic drugs (non-steroidal anti-inflammatory drugs, select antibiotics and antineoplastic agents); patients with a diagnosis of multiple myeloma; patients who had recently (<72 h) received intravascularly administered iodinated contrast media prior to the CECT; and patients involved in other research studies who may have altered the results of this study (*e.g.* drug trials).

## Sample size determination

The required sample size of patients who were representative of the population being studied to test the hypothesis that inflammation is a risk factor in CIN was determined using Schlesselman's formula for deriving prospective cohort sizes, which gave an *n* value of 193 per cohort.<sup>26</sup> A total of 386 patients were thus required to give a power of 80% and assuming an incidence of disease among the non-exposed of 3% (Figure 1).

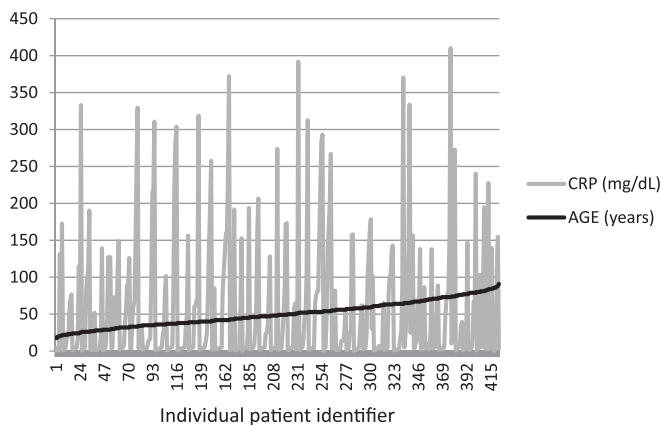
## Study procedures

CT technicians were trained to complete the questionnaires related to patient data and record the volumes of intravenous contrast administered to each patient. At the time of the procedure, the CT technician on duty explained the study details to the patient and obtained written consent. For patients who were unable to give informed consent, the next of kin were given the opportunity to do so in lieu of the patient. Where clarifications were required, the primary investigator was contacted and provided the required information. Each patient was assigned a study number and relevant information filled into the data collection form. Blood samples were drawn prior to administration of intravenous iodinated contrast by the primary investigator or qualified personnel, except in cases where the patient already had blood tests performed within 24 h. These samples were then used to assess the CRP and SCr levels. The patient then underwent the CECT as per standard protocol. Following completion of the CECT, the patient was informed of where and when she/he would return for the second blood sample if they were outpatients. For inpatients, routine blood tests were used or, where this was not available, blood samples were specifically drawn for the study. The second set of blood samples were submitted to the laboratory for SCr measurement.

## Data collection

Using data collection forms, each patient was assigned a unique study number. Descriptive patient data (age, sex, weight and height) were obtained from the patient at the time of the CECT scan and recorded in the data collection tool. Laboratory data were obtained from the patient records at the time of CECT scan

Figure 1. Age of patients relative to the amount of C-reactive protein (CRP).



and during the follow-up visit. Post SCr measurements were obtained from the laboratory 24–72 h after the post CECT SCr measurement was taken. Data entry was performed by the primary investigator and double checked for accuracy at the time of completion of data collection.

#### Data management and analysis

Data were entered into Microsoft Excel® v. 2010 (Microsoft, Redmond, WA) and analysed using Stata® software v. 12 for Windows (StataCorp LP, College Station, TX).

Once all the data had been entered into the spread sheet, data error identification was performed via frequency distribution tables to identify any out of range values. Where discrepancies arose (three patients), the data entry forms were used to resolve the error.

A  $\chi^2$  test was used to assess for relative risk of developing CIN given an ongoing inflammatory state.

Multiple logistic regression analysis was then performed to explore any independent determinants of outcome in the biophysical variables captured and volume of contrast administered that led to the development of CIN. The results were expressed as odds ratio (OR), with its respective 95% confidence interval (CI).

## RESULTS

423 patients were included in the study. Of these, 215 patients had elevated CRP and 208 normal CRP values.

The mean age of the sample population was 50 years with the youngest patients being 18 years of age and the eldest a 91-year-old female patient (Figure 1).

209 (49%) of the patients were male and 214 (51%) female.

The incidence of CIN in this study was 9.92%. Of the patients with inflammation, 29 (13.5%; CI, 8.90–18.07) developed CIN, while 13 (6.25%; CI, 2.96–9.54) of those without inflammation developed CIN (Table 1).

The multivariate regression analysis revealed that none of the biophysical variables (age, sex or weight) or the volume of

contrast administered (50, 100 and 150 ml converted by weight for volume to 17.5, 35.0 and 52.5 g, respectively) had any statistically significant association with development of CIN (Table 2).

## DISCUSSION

Iodinated contrast media are known to have two main classes of adverse effects: idiosyncratic and physiochemotoxic.<sup>27</sup>

The idiosyncratic adverse effects are also known as anaphylactoid reactions. They are not dose dependent and mimic anaphylactic (allergic) reactions via enzyme induction causing release of vasoactive substances, e.g. histamine and serotonin, and the subsequent activation of the complement system.

The physiochemotoxic reactions are postulated to result from the ability of iodinated contrast media to disrupt the body's homeostatic mechanisms, most notably the circulatory system. These reactions are largely owing to the physical and chemical effects of the contrast molecules and are thus considered dose dependent.

CIN is a physiochemotoxic adverse reaction to intravascular iodinated contrast that has varying definitions. The commonly applied definition is an absolute increase in SCr of 25% above the baseline within 24–48 h of intravascular iodinated contrast media without any other identifiable cause of the renal injury.<sup>3,4</sup> Although this definition is the most widely held, it is not without controversies.<sup>28</sup> SCr, for instance, can fluctuate to levels greater or lesser than 25% of a baseline reading without administration of iodinated contrast media. Furthermore, intrinsic renal damage can exist with “normal” SCr levels. Novel methods of identifying renal parenchymal damage exist (serum cystatin C), but these have not been validated in the assessment of CIN.<sup>29</sup>

Several studies have been performed that have established major risk factors for development of CIN. These include pre-existing renal injury, best identified by an elevated baseline SCr; nephrotoxic drug use; dehydration; administration of iodinated contrast media within 72 h preceding repeat contrast media dose; patients with multiple myeloma; and patients with sepsis.<sup>14</sup>

These risk factors are well established, and patients with one or more of these factors are considered high risk for development of CIN. Noting that patients with multiple myeloma and those with sepsis were both in prothrombotic state, it was hypothesized that the prothrombotic state contributed by the disease was responsible for the increased risk of developing CIN. Inflammation is known to be a prothrombotic state. This study thus sought to exclude patients with any identifiable risk factor from our study and subsequently divide the patients into two cohorts based on the presence or absence of ongoing inflammation as discerned by the patient's serum CRP level.

ILs are cytokines that are released by the immune system in both infectious and malignant states. Of the ILs, IL-6 and IL-12 have been implicated in altering the haemostatic mechanisms in primates and humans.<sup>18</sup> IL-6 is known to induce acute phase reactant production, notably CRP in the human liver.<sup>19,20</sup>

In this study, the cohort of patients who had a normal CRP measurement had an incidence of CIN of 6.25%, which is at the

Table 1. Incidence of contrast-induced nephropathy (CIN)

Descriptor	CIN	No CIN	Total	Incidence of CIN (%)
Inflammation	29	186	215	13.5
No inflammation	13	195	208	6.25
Total	42	381	423	9.92

Inflammation defined as an elevated C-reactive protein  $>5 \text{ mg dl}^{-1}$ .

upper end of the values described in other normal population studies of 2–5%. However, the patients who had elevated CRP measurements were noted to have a CIN incidence of 13.5%, giving a relative risk of 2.16.

Exploration of other biophysical variables and administration of dose of contrast were not associated with development of CIN. Interestingly, in our study, no association was found between age and development of CIN (OR, 1.01; CI, 0.99–1.03). This is unlike other studies that have found extremes of age to be an independent risk factor.<sup>21,30</sup> Part of the reason for this discrepancy may be owing to the relatively low numbers in this study (423) vs the numbers used to identify age as a risk factor (8357 for Mehran et al<sup>30</sup>). Furthermore, studies that have looked at age as an independent variable tend to be in high-risk populations, e.g. patients undergoing coronary intervention and thus likely to receive higher doses of iodinated contrast.

There was no association between the patient's weight, sex or administered volume of contrast and the development of CIN. Previous studies have not found any association between patient weight and CIN. This is largely because the administered volume of contrast is not directly proportional to the patient's body weight, but rather standardized for the type of diagnostic scan performed.

Cochran et al<sup>21</sup> performed a study that sought to identify various risk factors that had significant association with development of CIN. Although sex was found to have a significant OR of 3.2, multiple logistic regression analysis essentially ruled it out as an independent variable, as it was strongly associated with other more attributable risk factors. Other studies since then have only shown weak associations of sex with development of CIN. Our study had no association between patient's sex and development of CIN.

The dose of contrast administered in this study had no association with development of CIN. This is likely because the amount of contrast being administered was relatively low

(17.5–52.5 g = 50–150 ml) as opposed to interventional procedures that have varying and typically higher doses of contrast administered.<sup>31</sup> McCullough et al<sup>32</sup> also showed that the risk of CIN is minimal in patients receiving  $<100 \text{ ml}$  of contrast media.

The results of this study highlight a two-fold increased risk of developing CIN in patients with inflammation in the selected patient demographic.

#### Study limitations

The study was conducted in a private hospital setting where the majority of the clientele either have medical insurance or can afford to pay their healthcare costs in cash. This does not mirror the economic capacity of the country—and therefore the health-seeking behaviour—in which the study has been undertaken and as such, may not be generalizable.

Secondly, select inflammatory states do not exhibit a rise in CRP, e.g. scleroderma, polymyositis and dermatomyositis. As such, CRP cannot be reliably used to assess for inflammation in patients with these conditions. In such patients, use of cystatin C as a biomarker of renal injury can be considered. However, considering that these conditions are quite rare (e.g. scleroderma incidence is 19 cases per 1,000,000 in the USA), they are unlikely to have caused significant bias.

Thirdly, the study did not categorize the various causes of elevation of CRP, which limits the ability to assess for the effects of various inflammatory states, e.g. infection and malignancy on the development of CIN. A larger study with stratification of causes of inflammation may further elucidate the relationship between various inflammatory states and CIN.

#### CONCLUSION

This study demonstrated that the presence of inflammation increases the likelihood of development of CIN. This is the probable reason for the three-to-five fold increased incidence of CIN in the Kenyan population as compared with the developed world.

Table 2. Biophysical and inflammatory variables associated with contrast-induced nephropathy (CIN)

CIN	Odds ratio	Significance ( <i>p</i> )	95% confidence interval	
Inflammation	2.368307	0.016	1.177981	4.761435
Weight (kg)	0.990807	0.406	0.969441	1.012643
Sex (ref: male)	1.008584	0.980	0.524649	1.938900
Age	1.012129	0.225	0.992625	1.032016
Volume of contrast (ref: 50 ml)				
100 ml	1.341906	0.607	0.437445	4.116434
150 ml	1.315318	0.660	0.388184	4.456814



## RECOMMENDATIONS

From the results of this study, we recommend that in a patient with a known risk factor for CIN, assessment for detection of those with inflammation by use of a reliable biomarker (CRP in this study) can be used to generate a risk–benefit analysis prior to administration of iodinated intravenous contrast.

Furthermore, a larger study involving patients in public hospitals should be performed that would have results that are more generalizable.

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