High-Sensitivity C-Reactive Protein in Patients Undergoing Contrast Studies

José Carlos Carraro-Eduardo¹, Luis Guillermo Coca Velarde², Mariana Franco Ferraz Santino³, Diego Cerqueira Alexandre³, Danielle Calil de Sousa³, Iuna Almeida Deveza³

¹Universidade Federal Fluminense – Hospital Universitário Antônio Pedro – Serviço de Nefrologia – Niterói, RJ – Brazil
²Universidade Federal Fluminense – Instituto de Matemática – Departamento de Estatística – Niterói, RJ – Brazil
³Universidade Federal Fluminense – Curso de Graduação em Medicina – Niterói, RJ – Brasil

Abstract

Background: The use of iodinated agents in radiological studies can cause contrast-induced nephropathy (CIN) in the presence of classic risk factors such as previous renal disease and diabetes. High serum levels of high-sensitivity C-reactive protein (CRP) have been described as indicators of increased risk of CIN. Regardless of the occurrence of CIN, hs-CRP may rise after contrast studies.

Objective: To investigate the behavior of hs-CRP in patients undergoing parenteral administration of iodinated contrast agent.

Methods: Observational cross-sectional prospective study held at Hospital Universitário Antônio Pedro from 2007 to 2014 involving 51 patients, 30 men and 21 women, mean age 60.19±20.0, undergoing tests with low-osmolality contrast (Iopamidol 612 mg/ml).

Results: CIN occurred in 15 patients (29.4%). There was no correlation between increased hs-CRP and occurrence of CIN. The percentage increase in hs-CRP was significantly higher among patients undergoing cardiac catheterization (p=0.0044). The mean increase in hs-CRP in patients undergoing cardiac catheterization and in those submitted to administration of iodinated contrast by peripheral vein was 100.3% and 13.8%, respectively.

Conclusion: The findings suggest that increased hs-CRP after cardiac catheterization cannot be attributed to iodinated contrast agent.

Keywords: Contrast media; Inflammation; Cardiac catheterization; Acute kidney injury; Multidetector computed tomography

Introduction

The use of iodinated contrast is increasingly common. About 80 million/year diagnostic or therapeutic interventions are held with radiological contrast worldwide. In the United States, the number of coronary percutaneous invasive procedures increased by more than 300% in the last two decades. A serious complication from the use of these agents is the contrast-induced nephropathy (CIN). CIN is the third iatrogenic cause of acute renal failure in hospitalized patients and is associated with high mortality rate. Its incidence is variable and depends on the presence of risk factors, the type and quantity of contrast agent used, sensitivity, and the method employed for the diagnosis of renal involvement.

Vacuolation of epithelial cells of the renal proximal tubules follows the intravascular administration of iodinated contrast and the structural changes are...
reversible after a few days of its administration. It seems to be no correlation between the degree of vacuolization in the tubular cells and the intensity of functional renal damage. In prospective studies, the incidence of CIN ranged from 12-27%, but may reach more than 60% in patients with diabetic nephropathy with creatinine >3mg/dL.

Advanced age, heart failure, hypovolemia, renal failure, chronic liver disease, hyperuricemia, female sex and high contrast doses are often identified as risk factors for CIN and require a critical assessment of the risks and benefits for contrast-enhanced studies. When tests using contrast media are indispensable, protective measures should be used.

High serum levels of high-sensitivity C-reactive protein (hs-CRP) have been recently related to increased risk of CIN. hs-CRP is a protein of the acute phase and may also increase during chronic inflammatory processes.

Gao et al. demonstrated that the level of pre-procedure hs-CRP was a strong independent predictor for the risk of CIN in patients undergoing coronary angioplasty. Similar results were found by Jian-Wei et al., especially in those patients whose baseline hs-CRP was >6.50mg/L, which is also strongly associated with higher in-hospital mortality. Liu et al. noted that post-procedure hs-CRP is a useful independent predictor of CIN and was also significantly associated with in-hospital mortality in patients undergoing primary percutaneous coronary intervention.

Increased levels of hs-CRP after administration of iodinated contrast medium in cardiac catheterization procedures, regardless of the presence of CIN, was reported by Carraro-Eduardo et al. In an attempt to elucidate whether this increased hs-CRP had been caused by non-ionic iodinated contrast medium or by cardiac catheterization, patients submitted to administration of iodinated contrast by peripheral vein were compared with those undergoing catheterization.

### Methods

Observational cross-sectional prospective study was held with patients from Hospital Universitário Antônio Pedro, Universidade Federal Fluminense, from 2007 to 2014, to test the hypothesis that the increase in high-sensitivity C-reactive protein observed in hemodynamic tests is not related to the nonionic iodinated contrast medium, but to cardiac catheterization.

The study was approved by the Research Ethics Committee of Universidade Federal Fluminense under no. 081/06. All participants signed an Informed Consent Form according to Resolution CNS 466/12.

We evaluated 51 patients, 30 men and 21 women, mean age 60.19±20.0 (Table 1), hospitalized or treated at the HUAP outpatient clinic, scheduled to have the contrast test done.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=51)</th>
<th>HS (n=25)</th>
<th>CT (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women (n)</td>
<td>30/21</td>
<td>17/8</td>
<td>13/13</td>
</tr>
<tr>
<td>Age* (mean±SD)</td>
<td>60.19±20.0</td>
<td>57.3±13.2</td>
<td>60.2±10.2</td>
</tr>
<tr>
<td>Serum Cr (mg/dL)*</td>
<td>0.86±0.3</td>
<td>0.89±0.4</td>
<td>0.84±0.3</td>
</tr>
<tr>
<td>Baseline hs-CRP (mg/dL)*</td>
<td>1.99±2.0</td>
<td>2.59±5.2</td>
<td>1.39±2.0</td>
</tr>
<tr>
<td>Dyslipidemia (n)</td>
<td>22</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

HS – hemodynamic study; CT – computed tomography; Cr – creatinine; hs-CRP – high-sensitivity C-reactive protein; *values expressed as mean±standard deviation

Exclusion criteria were: pregnant women, presence of heart failure, hemodynamic instability, bacterial infections and chronic renal disease dependent on dialysis.

All patients underwent tests with low osmolality contrast (Iopamidol 612mg/mL). In 25 patients (HG = hemodynamics group), administration of nonionic iodinated contrast medium was done during cardiac catheterization (volume of 99.5±28.8mL); and in 26 patients (TG = tomography group), administration for computed tomography was done via peripheral vein (volume of 76.8±14.5mL). Serum creatinine (Jaffé method) and hs-CRP (particle-enhanced immunoturbidimetric assay) were
evaluated immediately before and 48 hours after administration of iodinated contrast.

Contrast-induced nephropathy was considered when there was relative increase of 25% or absolute increase of 0.5 mg/dL at baseline serum creatinine within 48 hours of exposure to iodinated contrast in the absence of an alternative cause³.

Statistical analysis was performed using the software S-Plus 8.0. To compare numeric data, Mann-Whitney test was used. In this study, p values <0.05 were considered statistically significant.

**Results**

Based on the nonparametric Wilcoxon-Mann-Whitney test, there was a statistically significant difference between the volumes of contrasts applied to patients from the hemodynamics and tomography groups (U=78.500; W=268.500; p-value=0.004).

The patients in the HG group received greater amounts of contrast than the TG group (Figure 1). CIN occurred in 15 (29.4%) patients, 9 from the TG. There was no correlation between higher levels of hs-CRP and the occurrence of CIN.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Biochemical profile after contrast test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS</td>
</tr>
<tr>
<td>Pre-test Cr (mg/dL)*</td>
<td>0.89 ±0.4</td>
</tr>
<tr>
<td>Post-test Cr (mg/dL)*</td>
<td>0.95 ±0.3</td>
</tr>
<tr>
<td>Cr variation*</td>
<td>0.06 ±0.2</td>
</tr>
<tr>
<td>Cr % variation</td>
<td>11.44</td>
</tr>
<tr>
<td>Pre-test hs-CRP (mg/dL)*</td>
<td>2.59 ±5.2</td>
</tr>
<tr>
<td>Post-test hs-CRP (mg/dL)*</td>
<td>3.25 ±5.4</td>
</tr>
<tr>
<td>hs-CRP variation*</td>
<td>0.65 ±1.0</td>
</tr>
<tr>
<td>hs-CRP % variation</td>
<td>100.32</td>
</tr>
</tbody>
</table>

HS – hemodynamic study; CT – computed tomography; Cr – creatinine; hs-CRP – high-sensitivity C-reactive protein; *values expressed as mean±standard deviation

**Discussion**

In this study, although the CIN occurred in 29.4% of patients, high levels of pre-procedure hs-CRP or hs-CRP increase after administration of iodinated contrast showed no correlation with renal injury.

In a study involving 165 patients undergoing primary percutaneous coronary intervention after myocardial infarction with ST-segment elevation, the incidence of CIN was significantly higher among patients with high hs-CRP¹⁶. Similar results were found in a retrospective study with 1452 patients⁷. This study involved a smaller number of patients with lower severity profile and lower medium levels of hs-CRP, which may explain this discrepancy in the results.

CIN is a serious adverse event from the use of nonionic iodinated contrast medium in cardiac catheterizations and is associated with increased morbidity and mortality³,⁵,⁶. Its pathophysiology is complex, involving direct cytotoxicity, oxidative stress and intrarenal hemodynamic changes⁴. The participation of inflammatory components in the genesis of CIN is not totally clear yet⁴.
A previous study had found that hs-CRP, an acute phase reactant in inflammatory processes, was significantly increased in patients undergoing cardiac catheterization, regardless of the occurrence of CIN\textsuperscript{20}.

There was a sevenfold increase of hs-CRP in the HG group than in the TG group. The average pre-procedural hs-CRP was not significantly different in both groups (p=0.5782). As the two groups were comparable and all patients underwent the same iodinated contrast agent, increased hs-CRP levels observed in patients undergoing catheterization seems to be a consequence of catheterization. While no patient has received any iodinated contrast agent levels exceeding 150 mL, average volumes of lopamidol were significantly higher in the HG group and this may be a limitation of this study.

The association between high hs-CRP and increased risk of acute kidney injury after iodinated contrast administration has been demonstrated by different authors\textsuperscript{7,16}. However, some studies demonstrate that hs-CRP increases routinely after iodinated contrast administration via cardiac catheterization and that this increase is a result of the contrast agent. Although a limitation in this study is that the average volume of contrast used in tests with arterial catheterization has been slightly larger than the one used in tests with administration of nonionic iodinated contrast via peripheral vein, it is a pioneer and is of clinical importance, since hs-CRP is an acute phase protein produced in the liver in response to tissue damage induced by various stimuli such as trauma, inflammation, infections and malignancies.

hs-CRP, more recently described, is able to detect much lower concentrations of hs-CRP (0.03 mg/L detection limit). Its importance was clearly demonstrated in JUPITER\textsuperscript{21,22}, involving 18,000 participants. In this study, statins reduced infarction and strokes in patients without heart disease or hypercholesterolemia, but with changes in the serum levels of hs-CRP\textsuperscript{21,22}. Not knowing that hs-CRP levels increase in invasive procedures such as cardiac catheterization may lead to misdiagnosis and inappropriate management.

### Conclusion

The results strongly suggest that the increase in hs-CRP observed after hemodynamic tests is not due to the contrast medium, but to the invasive cardiac catheterization procedure.

#### Potential Conflicts of Interest

This study has no relevant conflicts of interest.

#### Sources of Funding

This study had no external funding sources.

#### Academic Association

This study is not associated with any graduate programs.

### References


