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CORRESPONDENCE

Research Correspondence

Ultra-Low Contrast Volumes Reduce Rates of Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease Undergoing Coronary Angiography

To the Editor: Coronary angiography necessitates administration of iodinated contrast, which may precipitate an acute deterioration in renal function (contrast-induced nephropathy [CIN]). Predisposing factors include pre-existing chronic kidney disease and contrast volume, which to some extent can be controlled. However, there has been little investigation of the effect of contrast dose-response in patients undergoing diagnostic coronary angiography with very low doses (<50 ml). The objective of this study was to determine the incidence of CIN in a cohort of 185 patients with National Kidney Foundation stages 3 to 5 chronic, nondialysis-dependent kidney disease, undergoing diagnostic coronary angiography with iodinated contrast (iodixanol) between November 2003 to November 2005, and to investigate an association between contrast volume and CIN. Patients were excluded if they had systolic blood pressure <90 mm Hg, clinical shock, had no serum creatinine measurement within 1 week of angiography, or received intravenous contrast for other than diagnostic angiography (e.g., ventriculography, graft angiography, or intervention) or contrast either in the week preceding or following angiography. Statistical analyses included analysis of variance, Student *t* test, Pearson's chi-square test, Kaplan-Meier analysis with log-rank test, proportional hazard modeling (expressed as hazard ratio [HR] and 95% confidence intervals [CIs]), and multivariate logistic regression with stepwise techniques. Statistics are presented as mean ± standard deviation, or median with interquartile range (IQR). Significance was inferred at $p < 0.05$.

Sixty-eight percent of patients were men with a median age of 71 (IQR 60 to 78) years. Thirty-six percent had diabetes mellitus and 40% had left ventricular systolic dysfunction (mean left ventricular ejection fraction 50.1 ± 15%). All patients had an estimated glomerular filtration rate (eGFR) <60 ml/min. Median serum creatinine was 2.1 mg/dl (IQR 1.8 to 2.5), and mean eGFR was 31 ± 10 ml/min/1.73 m^2. Indications for coronary angiography included an abnormal stress test (40%), acute coronary syndrome (30%) before cardiac (valve) surgery (16%), and heart failure (14%).

All patients underwent standard diagnostic coronary angiography with a median contrast volume of 27 ml (IQR 20 to 50 ml), all with diagnostic quality images. The average procedure and fluoroscopy times were 15.2 ± 9 min and 4.2 ± 3 min. Biplane angiography was used in 114 patients (62%). All patients received pre-procedure hydration (typically 0.45% NaCl 2 mg/kg/h at least 2 h before, during, and 2 h after angiography) and 97% n-acetylcysteine. Significant obstructive coronary disease was found in 64%, 58% of whom had triple-vessel disease.

The average time to peak creatinine was 3.8 ± 3 days with creatinine measurements performed an average of 4.3 ± 3 times per patient within 1 week of angiography. Contrast-induced nephropathy defined as an absolute increase in serum creatinine ≥0.5 mg/dl within 7 days after the coronary angiogram occurred in 28 patients (15.1%). There were no baseline clinical factors in these patients that distinguished them from the overall cohort.

The occurrence of CIN after diagnostic coronary angiography was associated with an increased requirement for subsequent dialysis with an incident rate within 1 year of angiography of 53.6% (15 of 28) in those patients who developed CIN compared with 5.7% (9 of 157) in patients without CIN ($p < 0.0001$). By proportional hazard modeling, significant predictors of subsequent need for dialysis were CIN (HR 4.2 [95% CI 2.7 to 6.5], $p < 0.0001$) and baseline eGFR (incremental 10 ml/min—HR 0.45 [95% CI 2.8 to 6.8], $p = 0.0002$). Thirty-day mortality rates were 21.4% (6 of 28) in those patients who developed CIN compared with 3.2% (5 of 157) in patients without CIN ($p < 0.0001$). Factors associated with 30-day mortality included the occurrence of CIN (HR 2.74 [95% CI 1.5 to 5.1], $p = 0.002$) and age (incremental 10 years—HR 1.56 [95% CI 0.96 to 2.9], $p = 0.08$).

The volume of contrast administered was directly associated with the incidence of CIN. Volumes were higher in patients developing CIN (45 ± 18 ml) than those who did not (31 ± 18 ml, $p < 0.0005$). Those patients who received the lowest quartile of contrast volume were 7-fold less likely to develop CIN compared with those with the highest quartile of contrast volume (4.4% vs. 29.8%, $p = 0.005$) (Fig. 1). In multivariate analysis, the only significant factor associated with CIN was the volume of contrast administered, with each incremental 20 cc of contrast associated with an incremental odds ratio of 2.12 (95% CI 1.4 to 3.4, $p = 0.0002$).

Biplane angiography was used in 114 cases (62%) and was associated with a significant reduction in contrast volume (25 ± 13 ml vs. 47 ± 20 ml, $p < 0.0001$). The use of biplane angiography was not associated with either longer procedural times (14.9 ± 6 [biplane] vs. 15.6 ± 10 [monoplane] min, $p = 0.6$) or cumulative fluoroscopy (4 ± 2 [biplane] vs. 4.1 ± 4 (monoplane) min, $p = 0.4$) times. Those patients who had imaging with biplane angiography tended to have more diabetes (40.4% vs. 28.2%, $p = 0.09$) and worse renal function (eGFR 29 ± 11 ml/min/1.73 m^2 vs. 33 ± 9 ml/min/1.73 m^2, $p < 0.005$), both factors associated with an increased risk for CIN (1). Despite this apparent higher risk, the incidence of CIN among patients imaged with biplane angiography was significantly lower at 7.8% (9 of 114) compared with 26.8% (19 of 71, $p = 0.0007$) without the use of biplane. When adjusted for baseline eGFR, the use of biplane angiography was associated with a reduction in the rate of dialysis at 1 year after angiography ($p = 0.02$).

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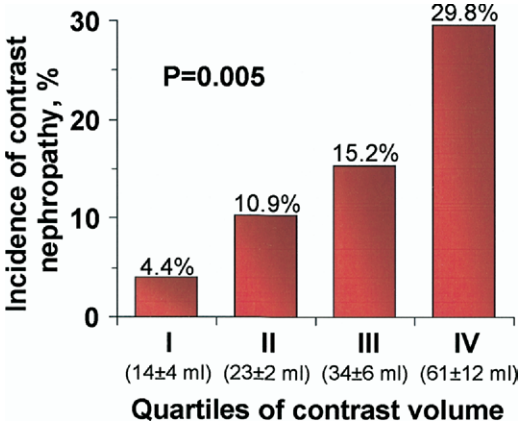

Figure 1 Contrast-Induced Nephropathy

Dose-dependent association of volume of administered contrast with the incidence of contrast-induced nephropathy ($p = 0.005$ by analysis of variance). Mean ± standard deviation of contrast volume for each quartile shown in parentheses.

The major finding of this study is that, as with procedures with higher volumes of iodinated contrast, patients with moderate-severe chronic kidney disease undergoing coronary angiography have an increased, contrast-volume dependent risk of CIN. Despite an elevated risk (1–3) and a high incidence of CIN, ultra-low volumes of contrast were associated with low rates of CIN. These findings have important implications concerning the referral of a patient with moderate-severe chronic kidney disease for diagnostic coronary angiography. With biplane imaging, studies can be performed with very low doses of iodinated contrast (without prolonging procedural times or radiation exposure), suggesting this technique may mitigate the risk of CIN in many patients at highest risk.

Our findings of a very low incidence of CIN with ultra-low doses of contrast are very encouraging, but some limitations of this study need to be considered. Our study was not randomized. While the major factor associated with CIN was contrast volume and the major factor associated with contrast volume was the use of biplane angiography, other factors need to be considered. The use of the iso-osmolar nonionic contrast medium, and that the vast majority received standard therapies of intravenous hydration and N-acetylcysteine likely contributed to a reduction in CIN. While patients had, on average, more than 4 serum creatinine measurements in the week after angiography, we cannot exclude the possibility that the peak measurement in some patients was not identified and hence the overall incidence of CIN was underestimated.

The current findings support the use of ultra-low-dose iodinated contrast facilitated by biplane angiography in patients at increased risk for contrast nephropathy referred for coronary angiography. Further studies will be required to assess the impact of low-dose contrast on the incidence of contrast nephropathy.

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Letters to the Editor

Age Predicts Cancer Incidence Better Than Statin-Induced Low-Density Lipoprotein Level

I disagree with the data analysis in the recently published article in the *Journal* suggesting an association between lower statin-induced low-density lipoprotein (LDL) levels and increased incidence of cancer (1). My analysis of the 8 larger and longer trials (>3 years and >1,000 patients) suggests a clear association between increasing age and increased incidence of cancer (Fig. 1) ($r^2 = 0.77$, $p = 0.004$, regression not corrected for study size). Age is a known and biologically plausible risk factor for cancer. Multivariate linear regression resulted in the following model:

$$\text{Yearly cancer incidence} = -1.103 - 0.012 \cdot \text{LDL on treatment} + 0.0614 \cdot \text{age}$$

The overall model was significant with $r^2 = 0.83$ and $p = 0.013$. The multivariate p value for the coefficient of age ($p = 0.055$) was nearly statistically significant and lower than the multivar-