**Background**—Few studies have investigated the safe limits of contrast to prevent contrast-induced nephropathy (CIN) based on hydration data. We aimed to investigate the relative safe maximum contrast volume adjusted for hydration volume in a population with a relatively low risk of CIN.

**Methods and Results**—The ratios of contrast volume-to-creatinine clearance (V/CrCl) and hydration volume to body weight (HV/W) were determined in patients undergoing cardiac catheterization. Receiver–operator characteristic curve analysis based on the maximum Youden index was used to identify the optimal cutoff for V/CrCl in all patients and in HV/W subgroups. Eighty-six of 3273 (2.6%) patients with mean CrCl 71.89±27.02 mL/min developed CIN. Receiver–operator characteristic curve analysis indicated that a V/CrCl ratio of 2.44 was a fair discriminator for CIN in all patients (sensitivity, 73.3%; specificity, 70.4%). After adjustment for other confounders, V/CrCl >2.44 continued to be significantly associated with CIN (adjusted odds ratio, 4.12; P<0.001) and the risk of death (adjusted hazard ratio, 2.62; P<0.001). The mean HV/W was 12.18±7.40. We divided the patients into 2 groups (HV/W ≤12 and >12 mL/kg). The best cutoff value for V/CrCl was 1.87 (sensitivity, 67.9%; specificity, 64.4%; adjusted odds ratio, 3.24; P=0.011) in the insufficient hydration subgroup (HV/W, ≤12 mL/kg; CIN, 1.32%) and 2.93 (sensitivity, 69.0%; specificity, 65.0%; adjusted odds ratio, 3.04; P=0.004) in the sufficient hydration subgroup (HV/W, >12 mL/kg; CIN, 5.00%).

**Conclusions**—The V/CrCl ratio adjusted for HV/W may be a more reliable predictor of CIN and even long-term outcomes after cardiac catheterization. We also found a higher best cutoff value for V/CrCl to predict CIN in patients with a relatively sufficient hydration status, which may be beneficial during decision-making about contrast dose limits in relatively low-risk patients with different hydration statuses. (Circ Cardiovasc Interv. 2015;8:e001859. DOI: 10.1161/CIRCINTERVENTIONS.114.001859.)

**Key Words:** diabetes mellitus ■ glomerular filtration rate ■ percutaneous coronary intervention

**Coronary Interventions**

**Safe Limits of Contrast Vary With Hydration Volume for Prevention of Contrast-Induced Nephropathy After Coronary Angiography Among Patients With a Relatively Low Risk of Contrast-Induced Nephropathy**

Yong Liu, MD; Ji-Yan Chen, MD; Ning Tan, MD; Ying-Ling Zhou, MD; Dan-Qing Yu, MD; Zhu-Jun Chen, MD; Yi-Ting He, MD; Yuan-Hui Liu, MD; Jian-Fang Luo, MD; Wen-Hui Huang, MD; Guang Li, MD; Peng-Cheng He, MD; Jun-Qing Yang, MD; Nian-Jin Xie, MD; Xiao-Qi Liu, MD; Da-Hao Yang, MD; Shui-Jin Huang, MD; Piao-Ye, MD; Hua-Long Li, MD; Peng Ran, MD; Chong-Yang Duan, MD; Ping-Yan Chen, MS

Contrast-induced nephropathy (CIN) may cause an increase in morbidity and even mortality in patients having this complication.1,2 Previous studies have suggested that CIN may be mainly associated with the dose of contrast medium used during cardiac catheterization and with renal function.3,4 Several previous studies have investigated the predictive value of the ratio of contrast media volume-to-creatinine clearance (V/CrCl) for CIN after percutaneous coronary intervention (PCI).5,6 A V/CrCl value >3.7 was found to be a significant independent predictor of an early (within 24 hour) abnormal increase in serum creatinine after PCI in a group of consecutive patients; this became 1 recommended method for evaluating the safe maximum volume of contrast.5 Studies from our group also indicated that V/CrCl >2.62 was a significant and independent predictor of CIN (within 48–72 hour) in consecutive patients undergoing PCI.6
WHAT IS KNOWN

• The contrast volume-to-creatinine clearance ratio is useful for predicting the maximum volume of contrast media that can be administered without significantly increasing the risk of contrast-associated nephropathy.

• Patients undergoing cardiac catheterization should receive adequate preparatory hydration (at least 12 hours postprocedural hydration at a speed of 1 mL/kg per hour), which serves as the standard therapy for the prevention of contrast-associated nephropathy.

WHAT THE STUDY ADDS

• The safe maximum volume of contrast administered during coronary angiography adjusted for hydration volume to body weight (sufficient hydration subgroup \(>12\) mL/kg or insufficient hydration subgroup \(\leq 12\) mL/kg) potentially serves as a more reliable predictor of contrast-induced nephropathy and even long-term outcomes.

• The contrast dose limits, nearly thrice the level of baseline creatinine clearance, can be less stringent in relatively low-risk patients with different hydration statuses.

Intravenous hydration with isotonic saline is the standard therapy for the prevention of CIN, and sufficient hydration may reduce its incidence.3–5 Therefore, we hypothesized that the optimal cutoff point of V/CrCl for evaluating the safe maximum volume of contrast may vary with the intravenous hydration volume (HV).

Methods

Subjects

This prospective observational study reviewed all consecutive patients who underwent coronary angiography or PCI between January 2010 and October 2012 according to the institutional protocol. As in a previous study6 and in the Predictive Value of Contrast Volume to Creatinine Clearance Ratio (PRECIMIN, ClinicalTrials.gov NCT01400295) study, we included patients aged \(\geq 18\) years who agreed to stay in the hospital for 2 to 3 days after coronary angiography. In accordance with the updated European Society of Urogenital Radiology Contrast Media Safety Committee guidelines,8 the exclusion criteria included pregnancy, lactation, intravascular administration of a contrast medium within the previous 7 days or 3 days post operation (n=83), no use of isotonic saline for hydration (n=18), diabetes mellitus, emergent PCI, age >75 years, and HV/W between the V/CrCl groups divided according to the cutoff value were also used to test the robustness of the results. Given the significant interaction between HV/W and V/CrCl with respect to CIN risk and the potential clinical application, the participants were stratified according to HV/W using 12 mL/kg as the cutoff value (insufficient hydration: HV/W<12 mL/kg; sufficient hydration: HV/W\(>12\) mL/kg). Univariable analyses of mortality were performed by log-rank test for patients categorized by baseline V/CrCl ratio. Multivariable Cox regression analyses were also performed, including the following factors: use of an intra-aortic balloon pump, CHF, anemia, hypotension, diabetes mellitus, emergent PCI, age group (>75 years). The data were analyzed on an available case basis and missing data were not imputed. All data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A 2-sided \(P<0.05\) was considered significant.

Results

All Patients

A total of 3273 consecutive patients (mean age, 63±11 years; 2503 men) with a relatively low risk of CIN who underwent coronary angiography (mean contrast volume, 128±67 mL; mean, CrCl 71.9±27.0 mL/min) were included in the study. The patients’ HV/W levels were correlated with CrCl \((r=0.417; P<0.001)\). On postcontrast exposure days 1, 2, and 3, at least 1 serum creatinine value was available for all of
The participants, at least 2 values were available for 45.6% (1493/3273) of patients, and 3 values were available for 11.7% (383/3273) of the patients.

Eighty-six of the 3273 (2.6%) patients developed CIN. ROC curve analysis showed correlation between the V/CrCl ratio and CIN, with a C-statistic of 0.780. ROC curve analysis and the Youden index showed that the best cutoff level of V/CrCl was >2.44, which exhibited 73.3% sensitivity and 70.4% specificity for predicting CIN (Figure 1). The incidence of CIN was 6.26% (63/1007) in patients with V/CrCl >2.44 and 1.02% (9/1352) in patients with V/CrCl ≤2.44. A comparison of the baseline characteristics of subgroups defined by the V/CrCl ratio using this cutoff value (Table 1), revealed that patients with a higher V/CrCl ratio (>2.44) were more likely to be older, to have anemia or CHF, to be hypertensive, with lower left ventricular ejection fraction and hemoglobin values, a high contrast volume, and a longer procedure duration. They more frequently presented with emergent PCI or multivessel disease and were treated with more stents. Furthermore, they were more likely to have a higher risk Mehran score (7.12±4.51 versus 4.52±3.85; P<0.001) was significantly and independently related to the risk of CIN (Figure 2). The CIN rates were 2.49% (19/762) in patients with V/CrCl>1.87 and 0.67% (9/1352) in patients with V/CrCl ≤1.87. The propensity score analysis showed that the relationship between V/CrCl>1.87 and HV/W>12 mL/kg was significantly and independently related to the risk of CIN (OR, 3.08; 95% CI, 1.55–6.14; P<0.001).

Multivariable logistic regression was then performed, including V/CrCl >2.44 and other clinical and procedural variables. The results of this analysis showed that a V/CrCl >2.44 (OR, 4.16; 95% confidence interval [CI], 2.45–7.06; P<0.001) was significantly and independently related to the risk of CIN (Figure 2). The propensity score analysis showed that the result was robust (OR, 3.24; 95% CI, 1.31–8.00; P=0.011) was significantly and independently related to the risk of CIN (Figure 2). The CIN rates were 2.49% (19/762) in patients with V/CrCl>1.87 and 0.67% (9/1352) in patients with V/CrCl ≤1.87. The propensity score analysis showed that the relationship between V/CrCl>1.87 and HV/W>12 mL/kg was significantly and independently related to the risk of CIN (OR, 3.08; 95% CI, 1.55–6.14; P<0.001).
and CIN was not significant because of the small number of CIN events (OR, 1.78; 95% CI, 0.51–6.03; \(P=0.370\)).

**HV/W>12 mL/kg**

CIN developed in 5.0% (58 of 1101 patients) of patients with HV/W >12 mL/kg, ROC curve analysis showed a correlation between the V/CrCl ratio and CIN, with a C-statistic of 0.732. ROC curve analysis showed that, at a cutoff level of >2.93, the V/CrCl ratio exhibited 69.0% sensitivity and 65.0% specificity for predicting CIN. Multivariable logistic analysis showed that V/CrCl >2.93 (OR, 3.04; 95% CI, 1.64–5.63) was significantly and independently related to the risk of CIN, \((P<0.001; \text{Figure 2})\). The CIN rates were 9.41% (40/425) in patients with V/CrCl>2.93 and 2.45% (18/734) in patients with V/CrCl\(\leq2.93\). The propensity score analysis showed that the result was robust (OR, 3.43; 95% CI, 1.53–7.69; \(P<0.001\)).

The optimum cutoff value for the V/CrCl ratio was higher in patients with HV/W \(\geq12\) mL/kg than in those with HV/W <12 mL/kg (2.93 versus 1.87).

![Figure 2](http://circinterventions.ahajournals.org/Downloaded from)
Follow-Up
The mean follow-up period was 2.51±0.86 years (median, 2.45; interquartile range, 1.80–3.27 years) and data were available for all who survived to discharge. On log-rank analysis, patients with a high V/CrCl ratio (>2.44) presented a worse survival rate than patients with V/CrCl \( \leq 2.44 \) (\( P < 0.001 \); Figure 3A), so did the patients with CIN (\( P < 0.001 \); Figure 3B). Similar trends were observed among those patients with HV/W \( \leq 12 \) mL/kg and HV/W >12 mL/kg at presentation; the respective cutoff points for V/CrCl were 1.87 and 2.93, respectively.

On multivariable Cox proportional hazard regression analysis, the risk of death or major adverse clinical events was higher for patients with a high V/CrCl ratio (Figures 4 and 5). Cox regression analysis indicated that V/CrCl ratio, age, diabetes mellitus, CHF, hypotension, intra-aortic balloon pump use, hypertension, anemia, and emergent PCI were significant risk factors for death after PCI (Figure 4).

Discussion
This study may be the first to attempt to determine safe V/CrCl cutoff values for different hydration strengths with a view to avoiding CIN after coronary angiography. The HV may influence the safe limits of contrast dose during the procedure; taking this into account could reduce the risk of CIN. More severe limits for contrast dose should be applied in patients with a high V/CrCl ratio (Figures 4 and 5). Cox regression analysis indicated that V/CrCl ratio, age, diabetes mellitus, CHF, hypotension, intra-aortic balloon pump use, hypertension, anemia, and emergent PCI were significant risk factors for death after PCI (Figure 4).

In a previous study, Marenzi et al defined the contrast ratio as the ratio between the contrast volume administered and the maximum recommended contrast dose (MRCD), and they showed that patients who received more than the MRCD had a more complicated in-hospital course and a higher CIN incidence (35% versus 6%; \( P < 0.001 \)) after primary PCI than patients who were administered less than the MRCD. In another registry of >16000 PCI cases, exceeding the calculated MRCD was found to be the strongest independent predictor of nephropathy requiring dialysis in patients undergoing elective coronary interventions. Patients who received a volume of contrast that exceeded the MRCD were 6× more likely to develop this complication. Thus, the amount of contrast medium is an important risk factor for CIN.

The CIN risk score increased significantly as the V/CrCl ratio increased. Because the V/CrCl ratio has been shown to correlate with the area under the curve of contrast medium concentration over time and represents both the dose of contrast medium and renal function, this index should more closely predict the safety profile of contrast media compared with the absolute volume of contrast alone, particularly with respect to the risk of CIN. The different cutoff values for V/CrCl and the incidence of CIN found in different studies may be the result of different definitions of CIN (48–72 or 24 hours), diabetes mellitus, or acute myocardial infarction. Gurm et al also found that the use of a high contrast dose is associated with increased risks of CIN and nephropathy requiring dialysis across the continuum of baseline predicted risk and calculated CrCl. A high ratio of volume to glomerular filtration rate is associated with increased in-hospital and long-term mortality in patients with ST-elevation myocardial infarction undergoing primary PCI.20 Our previous study showed that a planned V/CrCl ratio <3.7, and preferably <2.62, might be valuable in reducing the risks of CIN and even death after PCI.21 A large step in cumulative mortality was noted \( \approx 2 \) years after the procedure. This observation might be attributable to the follow-up protocol; we performed office visits and telephone interviews at 1, 6, 12, and 24 months after the procedure.

However, there is little evidence that hydration affects the cutoff value of the V/CrCl ratio. Hydration remains the cornerstone of CIN prevention. It produces an expansion of plasma volume with concomitant suppression of the renin–angiotensin–aldosterone system, downregulation of tubuloglomerular...
feedback, dilution of contrast media, and thus prevention of renal vasoconstriction and tubular obstruction.\textsuperscript{23,24} The guidelines recommend that intravenous hydration with 1 mL/kg per hour (0.5 mL/kg per hour if left ventricular ejection fraction <35% or New York Heart Association >2) should be started 12 hours before and continued for 24 hours after the procedure to prevent CIN in patients with chronic kidney disease.\textsuperscript{7,8} The guidelines for the prevention of CIN noted that intravenous hydration should be administered for 12 hours after the procedure according to weight (1 mL/kg per hour).\textsuperscript{10,11} On the basis of calculation, patients should receive hydration using a volume >12 mL/kg (HV/W>12 mL/kg). The mean HV/W was coincidentally 12 mL/kg in our study. We stratified the patients into 2 groups, such as HV/W\leq12 mL/kg and HV/W>12 mL/kg (relative sufficient hydration based on protocols from studies cited by clinical guideline recommendations)\textsuperscript{30,11} as this division also made.

Maioli et al\textsuperscript{25} reported that sufficient intravenous volume expansion may prevent contrast-induced acute kidney injury in patients undergoing primary PCI. These data were derived from 450 ST-segment–elevation myocardial infarction patients who were randomly assigned to receive different hydration strategies (mean HV, 1157 mL versus 885 mL; \(P<0.001\)): the incidence of CIN was 12% versus 22.7%, respectively. Marenzi et al,\textsuperscript{26} in a randomized controlled trial of 170 patients with chronic kidney disease undergoing coronary procedures, reported that sufficient hydration significantly reduced the risk of CIN (4.6% versus 18%; \(P=0.005\)). Announcing the results of the Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial, Brar\textsuperscript{27} reported that sufficient hydration might reduce the incidence of CIN (6.7% versus 15.7%; \(P=0.008\)) compared with standard hydration (median HV, 1711 mL versus 807 mL). However, most studies investigating the safe volume of contrast lacked information

Figure 4. Multivariable Cox regression analysis indicated that a volume-to-creatinine clearance (V/CrCl) ratio>2.44 was significantly associated with an increased risk of death (A: hazard ratio [HR], 2.71; 95% confidence interval [CI], 1.90–3.87; \(P<0.001\)) and major adverse clinical events (B: HR, 1.42; 95% CI, 1.21–1.68; \(P<0.001\)) after coronary angiography. CHF indicates chronic heart failure; and PCI, percutaneous coronary intervention.

Figure 5. Unadjusted (U) and adjusted (A) hazard ratios for death (A) or major adverse clinical events (MACE; B) among all patients and subgroups including patients with hydration volume to body weight (HV/W)\leq12 mL/kg and patients with HV/W>12 mL/kg, with volume-to-creatinine clearance ratio cutoffs of 2.44, 1.87, and 2.93. HR indicates hazard ratio.
about hydration.\textsuperscript{5,18,19,20} We found that sufficient hydration significantly improved the optimal cutoff value of V/CrCl (2.93 versus 1.87) for CIN. This implies that looser limits of contrast dose may be applied in patients with sufficient hydration, according to the patients’ actual requirement.

A large collaborative registry that included 58,957 patients undergoing PCI suggested that the definition of CIN (a rise in creatinine of $\geq 0.5$ mg/dL) in patients undergoing PCI is superior to $\geq 25\%$ increase in Cr for identifying patients at greater risk of adverse renal and cardiac events.\textsuperscript{20} In addition, the combined CIN (increase of $\geq 25\%$ or absolute 0.5 mg/dL creatinine levels) was not significantly correlated with long-term mortality in patients without CKD ($\geq 60$ mL/min per 1.73 m$^2$).\textsuperscript{20} Therefore, we used the definition of an increase of 0.5 mg/dL in patients with relative preserved renal function. The overall risk level of the studied group was low, as reflected by the high baseline creatinine clearance (mean, 71.89 mL/min) and the low Mehran score for the overall incidence of CIN (2.6%). Because of the small sample size, the low rate of CIN and the low proportion of high-risk patients (severe renal dysfunction, elderly patients, or PCIs), we did not have sufficient data to investigate the relative safe maximum volume of contrast (V/CrCl) in relation to hydration status in high-risk patients with adequate statistical power. We are conducting 3 prospective trials with different strict and useful hydration protocols in high-risk patients, with a view to verifying the findings of this study.

In this study, the incidence of CIN was higher in the sufficient hydration group than in the insufficient hydration group, because the level of HV/W was correlated with patients’ CrCl ($r=-0.414; P<0.001$). In addition, according to the guidelines, patients with chronic kidney disease or low baseline CrCl are at particularly high risk of CIN and require preventive measures, including a high level of periprocedural hydration. However, despite significant advances in the identification of risk as well as therapeutic approaches for risk reduction, CIN is not preventable in the high-risk patient who requires contrast administration. Last but not least, residents may continue hydration in those patients who develop CIN in spite of sufficient hydration.

In this study, patients with a higher HV/W ratio exhibited a higher safe V/CrCl cutoff value, according to a safe optimized MRCD formula: CrCl$\times$optimal safe ratio; this suggests that looser limits of contrast dose could be applied in patients who have sufficient hydration.

**Study Limitations**

This study has several limitations. First, because this prospective, observational study was conducted in a single center, the evidence may not be as strong as in a randomized controlled trial. Second, the CrCl was computed using the Cockcroft–Gault formula, rather than a direct measurement. Third, variations in our measurement times may have resulted in not capturing postprocedure peak creatinine levels. Furthermore, 50\% of the patients were discharged 2 days after the coronary angiography, so serum creatinine concentrations were not measured on day 2 in these patients. This variation and lack of measurement data may have led to an underestimation of the true incidence of nephropathy in this study population. However, the results of a separate analysis for patients with multiple creatinine measurements (45.6\%; 1493/3273) are similar to that for all the patients (with at last 1 postprocedure creatinine) despite the relatively higher CIN incidence (5.06\%). Fourth, the incidence of CIN, which served as the primary end point, was low. In addition, the study included few high-risk patients (severe renal dysfunction, advanced age); therefore, we did not have adequate data to investigate the contrast limit in high-risk patients. This may limit the implications of our results, and studies using high-risk patients may be needed in the future. Fifth, bad patient compliance resulted in a high rate of those lost to follow-up, 22\% at 1 year, which may have affected the results about clinical adverse outcomes during follow-up, and may have influenced the significance of the analysis. However, this may also supply defective data as references to understand the long-term prognosis. Finally, we used HV/W as a measure of weight-adjusted HV determined by different doctors based on their individual experience, as well as different patient and procedural characteristics. No uniform protocol for intravenous hydration was not strictly applied in this observational study. The propensity score analyses in our study were used as sensitivity analysis of the multivariable logistic regression analyses that addressed the problem relating to the nonrandomization of volume infusion. In clinical practice, the contrast dose was left to the discretion of the interventional cardiologist, which was also highly associated with the risk of CIN. Therefore, more randomized trials with different useful hydration protocols may be required to reduce the bias in the future.

**Conclusions**

Individual relatively safe maximum volumes of contrast during coronary angiography adjusted for different HVs may be more reliable and may have significance for the long-term prognosis in these patients. We also found a higher best cutoff value for V/CrCl to predict CIN in patients with a relatively sufficient hydration status, which may be beneficial during decision-making about contrast dose limits in relatively low-risk patients with different hydration statuses.

**Sources of Funding**

This study was supported by a grant from the Science and Technology Planning Project of Guangdong Province (grant no. 2008A030201002), Guangdong Cardiovascular Institute; Guangdong Provincial Cardiovascular Clinical Medicine Research Fund (grant no. 2009X41). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the article; the work was not funded by any industry sponsors.

**Disclosures**

None.

**References**


Safe Limits of Contrast Vary With Hydration Volume for Prevention of Contrast-Induced Nephropathy After Coronary Angiography Among Patients With a Relatively Low Risk of Contrast-Induced Nephropathy

Yong Liu, Ji-Yan Chen, Ning Tan, Ying-Ling Zhou, Dan-Qing Yu, Zhu-Jun Chen, Yi-Ting He, Yuan-Hui Liu, Jian-Fang Luo, Wen-Hui Huang, Guang Li, Peng-Cheng He, Jun-Qing Yang, Nian-Jin Xie, Xiao-Qi Liu, Da-Hao Yang, Shui-Jin Huang, Piao- Ye, Hua-Long Li, Peng Ran, Chong-Yang Duan and Ping-Yan Chen

Circ Cardiovasc Interv. 2015;8:
doi: 10.1161/CIRCINTERVENTIONS.114.001859
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/8/6/e001859

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/