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Volume-to-Creatinine Clearance Ratio

A Pharmacokinetically Based Risk Factor for Prediction of Early Creatinine Increase After Percutaneous Coronary Intervention

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Objectives This study sought to validate a pharmacokinetically derived measure of the risk of an early increase in serum creatinine after percutaneous coronary intervention (PCI).

Background The ratio of the volume of contrast media to the creatinine clearance (V/CrCl) has been shown to correlate with the area under the curve of contrast media concentration over time.

Methods We calculated V/CrCl in 3,179 consecutive patients undergoing PCI. An increase in serum creatinine of >0.5 mg/dl by 24 to 48 h was considered abnormal. Receiver-operator characteristic methods were used to identify the optimal sensitivity and specificity for the observed range of V/CrCl. The predictive value of V/CrCl for the risk of an early increase in creatinine was assessed using multivariable logistic regression.

Results The overall incidence of an abnormal, early increase in creatinine was 1.5%. The mean and median values of V/CrCl for patients with (mean 5.2 ± 4.4, median 4.3, interquartile range 2.7 to 6.0) and without (mean 3.0 ± 2.0, median 2.5, interquartile range 1.7 to 3.8) an early creatinine increase were each significantly ($p < 0.001$) different between groups. Furthermore, there was a significant association between V/CrCl and an early increase in creatinine (overall and trend, $p < 0.001$). The receiver-operator characteristic curve analysis indicated that a V/CrCl ratio of 3.7 was a fair discriminator for the early creatinine increase (C-statistic 0.69). After adjusting for other known predictors of post-PCI creatinine increase, V/CrCl ≥3.7 remained significantly associated with an early abnormal increase in serum creatinine (odds ratio 3.84; 95% confidence interval 2.0 to 7.3, $p < 0.001$).

Conclusions A V/CrCl ratio >3.7 was a significant and independent predictor of an early abnormal increase in serum creatinine after PCI in this unselected patient population. (J Am Coll Cardiol 2007;50:584–90) © 2007 by the American College of Cardiology Foundation

Radiographic contrast media-associated nephrotoxicity (CAN) is responsible for approximately 11% of all iatrogenic renal insufficiency and is the third most common cause of hospital-acquired renal failure (1). Contrast media-associated nephrotoxicity is traditionally defined as an increase in serum creatinine of either 0.5 mg/dl or 25% from baseline within 72 h of exposure (2,3). The association of the above-specified magnitude and time course of serum creatinine increase with short- and long-term adverse clinical outcomes is well established (4–6). Given that the majority of patients currently undergoing invasive cardiovascular procedures are either outpatients or are likely to be discharged within 24 h after the procedure (7), assessment of changes in serum creatinine beyond 24 h often is problematic. Therefore, a practical means of predicting an early postprocedural increase in creatinine would be of clinical benefit. Although underlying renal insufficiency and diabetes mellitus are known risk factors for the development of CAN (8,9), the precise role of the volume of contrast administered has yet to be established (9–14).

In pharmacokinetic terms, systemic exposure to a drug (and, therefore, its safety and efficacy profile) is best quan-

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tified by the area under the drug's blood concentration versus time curve (15). Recently, the derivation and validation of V/CrCl as a surrogate for the area under the curve has been reported in normal volunteers (16). We hypothesized that this index would be useful in the prediction of an abnormal increase in post-percutaneous coronary intervention (PCI) creatinine and that this index would show better predictive performance over considerations of volume or underlying renal function alone (6,8,9,11,12). We tested this hypothesis prospectively in an unselected population of patients undergoing PCI.

Methods

Theoretical background. Systemic exposure to a drug is best assessed by quantifying the area under the blood concentration versus time curve. Contrast media are distributed and eliminated consistent with a linear model (17,18). Systemic clearance of a drug is equal to the ratio of the following time-dependent variables: the rate of elimination, dX/dt(t), and the blood drug concentration, C(t). Thus,

$$Clearance = \frac{dX/dt(t)}{C(t)} \quad [1]$$

Integrating numerator and denominator in Equation 1 yields:

$$Clearance = \frac{\int (dX/dt)dt}{\int C(t)dt} = \frac{Total\ Dose}{AUC} \quad [2]$$

Rearranging Equation 2 yields:

$$AUC = \frac{Total\ Dose}{Systemic\ Clearance} \quad [3]$$

Therefore, systemic exposure (area under the curve) is directly related to dose and inversely related to systemic clearance. For contrast media exposure, the volume of contrast injected is equal to the total dose. Because contrast media are renally excreted in an unmetabolized state (19), their systemic clearance can be approximated by the creatinine clearance. Thus, the area under the blood concentration versus time curve can be approximated by the total volume of contrast given divided by creatinine clearance (CrCl):

$$AUC \sim \frac{Volume}{CrCl} \quad [4]$$

Patient population. The present study population is composed of consecutive patients enrolled in the National Heart, Lung, and Blood Institute Dynamic Registry undergoing PCI in recruitment waves 4 (February 2004 to May 2004) and 5 (February 2006 to August 2006). The Dynamic Registry is a multicenter registry (25 clinical centers in the U.S. and Canada) whose purpose, structure, and function have been previously reported (20,21). Data collected include patient history, demographics, and procedural details including the total volume of contrast administered and in-hospital adverse events. In combined waves 4 and 5 (n = 4,093), after excluding patients with no recorded contrast volume (n = 107), those on dialysis (n = 125), those without paired creatinine determinations (n = 649), and those without recorded weight or age (n = 33), data from 3,179 patients were available for the present analysis. An increase in creatinine from baseline of >0.5 mg/dl after PCI was considered abnormal. The volume (V) to creatinine clearance (CrCl) ratio, an estimate of contrast media area under the curve, was calculated by dividing the volume of contrast received by the patient's CrCl. The CrCl was estimated using the Cockcroft-Gault method (22): CrCl (ml/min) = 140 − age (years) × weight (kg)/72 × serum creatinine (mg/dl) {× 0.85 for female subjects}.

Abbreviations and Acronyms

CAN = contrast media-associated nephrotoxicity
CrCl = creatinine clearance
PCI = percutaneous coronary intervention

Statistical analysis. Crude incidence rates for in-hospital adverse events and abnormal post-PCI creatinine increases were calculated. Continuous explanatory variables were categorized into either accepted cut points (e.g., decades for age) or into tertiles (e.g., contrast volume). Odds ratios and 95% confidence intervals were calculated using logistic regression. Additionally, continuous variables are summarized as mean ± SD or medians and interquartile ranges and compared using the Wilcoxon rank sum test. Receiver-operator characteristics analysis was used to determine the optimal cut point for V/CrCl in this population using SPSS (version 14.0, SPSS Inc., Chicago, Illinois). Logistic regression was used to model the association between the V/CrCl cut point (identified by the receiver-operator characteristics analysis) and an abnormal increase in creatinine. Risk factors were initially screened for univariate association with an abnormal increase in creatinine at $p < 0.20$, and identified variables were then assessed in a forward stepwise manner using a p value criterion of ≤0.05. The final model includes the volume/clearance ratio and other important baseline characteristics and is also adjusted for age and diabetes mellitus. The goodness-of-fit assumption was assessed using the Hosmer-Lemeshow method and satisfied when $p > 0.05$. Statistical significance for all comparisons was defined when $p < 0.05$.

Results

The mean age for the entire population was 64 ± 12 years; the mean body mass index was 29.5 ± 6.4 kg/m^2; the mean creatinine clearance was 86.9 ± 38.2 ml/min; and the mean estimated glomerular filtration rate (using the Modification of Diet in Renal Disease method) was 74.8 ± 25.1 ml/min.

Postprocedural creatinine values were available in 92.8% of patients at 24 h and in an additional 6.8% from 24 h and 48 h. The overall incidence of an abnormal increase in creatinine, as previously defined, was 1.5%.

As seen in Table 1, older patients (70 to 79 years and ≥80 years) were significantly more likely to develop an early increase in creatinine compared with patients <60 years. The mean age for those without an increase in creatinine was 63.9 ± 12 years and 69.9 ± 12 years for those with a creatinine increase ($p < 0.001$). There was no association between this early increase in creatinine and gender. Patients with a creatinine increase were more likely to have a lower body mass index (mean 27.5 ± 4.8) compared with those without an increase in creatinine (mean 29.5 ± 6.4; $p = 0.02$). Compared with white patients, black patients were 2.3 times more likely to develop an early increase in creatinine. Patients with a history of concomitant disease, (e.g., congestive heart failure, chronic kidney disease [defined historically in the Dynamic Registry], cerebrovascular disease, or diabetes mellitus) all had a significant or near significant higher risk of early creatinine increase. The mean baseline creatinine in those patients with a history of chronic kidney disease was significantly higher than those without a history of chronic kidney disease (1.85 ± 0.87 vs. 1.05 ± 0.28, respectively; $p < 0.001$). Lower values for CrCl were associated with a higher risk for post-PCI

Table 1 Univariate Association of Patient Demographics and Cardiac Risk Factors With an Early Abnormal Creatinine Increase After Percutaneous Coronary Intervention

Factor	Number of Patients	Incidence (%)	Odds Ratio	95% Confidence Interval	p Value
Age (yrs)					
<60	1,218	0.8	1.0	Reference	—
60–69	869	1.0	1.26	0.51–3.12	0.61
70–79	799	2.0	2.47	1.11–5.47	0.03
≥80	293	4.4	5.61	2.43–12.92	<0.001
Body mass index (kg/m^2)					
<25.0	695	1.9	1.0	Reference	—
25.0–29.9	1,219	2.0	1.05	0.53–2.08	0.88
≥30.0	1,259	0.9	0.46	0.21–1.04	0.06
Gender					
Male	2,155	1.5	1.0	Reference	—
Female	1,024	1.6	1.05	0.57–1.93	0.87
Race					
White	2,499	1.2	1.0	Reference	—
Black	521	2.9	2.37	1.27–4.43	0.007
Other	147	1.4	1.10	0.26–4.66	0.89
History of congestive heart failure					
No	2,814	1.2	1.0	Reference	—
Yes	296	4.7	4.06	2.15–7.66	<0.001
Congestive heart failure on admission					
No	2,943	1.3	1.0	Reference	—
Yes	223	4.5	3.59	1.76–7.30	<0.001
Chronic kidney disease					
No	2,948	1.2	1.0	Reference	—
Yes	231	5.2	4.43	2.27–8.64	<0.001
Peripheral vascular disease					
No	2,912	1.4	1.0	Reference	—
Yes	267	2.2	1.57	0.66–3.73	0.31
Cerebrovascular disease					
No	2,924	1.4	1.0	Reference	—
Yes	255	3.1	2.33	1.08–5.04	0.03
Pulmonary disease					
No	2,921	1.4	1.0	Reference	—
Yes	258	2.3	1.63	0.69–3.88	0.27
Diabetes					
No	2,113	1.2	1.0	Reference	—
Yes	1,061	2.1	1.70	0.96–3.01	0.07
Creatinine clearance (ml/min)					
<30	81	4.9	6.06	2.02–18.15	0.001
30–59	745	3.2	3.88	2.13–7.07	<0.001
≥60	2,353	0.8	1.0	Reference	—

creatinine increase. The mean CrCl in patients with an early increase in creatinine was significantly lower (67.6 ± 41.5 ml/min) compared with patients without an increase in creatinine (87.2 ± 38.1 ml/min; $p < 0.001$) as was the estimated glomerular filtration rate (69.5 ± 42.9 ml/min vs. 74.9 ± 24.7 ml/min; $p = 0.006$).

Procedural characteristics are shown in Table 2. There was no association between the total volume or type of contrast media (nonionic low osmolar, nonionic iso-osmolar, ionic high osmolar, ionic low osmolar) and an early creatinine increase. The significant association between an abnormal creatinine increase and periprocedural hydration likely reflects the use of the latter more often in subjects at risk of CAN. There was a borderline significant difference in the total volume of contrast administered to those with (255 ± 124 ml) and without (224 ± 112 ml; $p = 0.06$) the early increase in creatinine.

As seen in Table 3, patients with an early creatinine increase had lower rates of angiographic and procedural success and a significantly higher incidence of postprocedural complications; specifically, bleeding requiring transfusion, death, and death or myocardial infarction. The overall incidence of any major adverse clinical event (defined as death, myocardial infarction, or coronary bypass surgery) was significantly higher in the patients with an early abnormal creatinine increase.

The mean V/CrCl ratio was 3.0 ± 2.0 in patients without a creatinine increase and 5.2 ± 4.4 in patients with an increase in creatinine ($p < 0.001$), whereas the median V/CrCl ratios for those without and with CAN were 2.5 (interquartile range 1.7 to 3.8) and 4.3 (interquartile range 2.7 to 6.0), respectively ($p < 0.001$). There was a significant association between higher V/CrCl ratio values and the risk of an early increase in creatinine (Fig. 1). The distribution of values for V/CrCl in patients with and without an early, abnormal increase in creatinine is shown in Figure 2.

Receiver-operator characteristic curve analysis showed fair discrimination between patients with and without an early increase in creatinine (C-statistic of 0.69) at a V/CrCl ratio of 3.7 (Fig. 3). At this value, the sensitivity and specificity for detection of an early, abnormal post-PCI creatinine increase were 65% and 75%, respectively.

Univariate logistic regression indicated that V/CrCl was a highly significant predictor of an early abnormal creatinine increase (odds ratio 5.06; 95% confidence interval 2.79 to 9.20). Multivariable analysis indicated that a V/CrCl ≥3.7 was significantly and independently related to the risk of an

Table 2 Univariate Association of Procedural Characteristics With an Early Abnormal Creatinine Increase After PCI

Factor	Number of Patients	Incidence (%)	Odds Ratio	95% Confidence Interval	p Value
Acute MI					
No	2,180	1.3	1.0	Reference	—
Yes	999	2.0	1.57	0.88–2.80	0.13
Intravenous hydration before PCI					
No	2,631	1.6	1.0	Reference	—
Yes	534	2.6	2.06	1.10–3.86	0.02
Contrast volume (ml)					
≤169	1,049	1.0	1.0	Reference	—
170–249	1,036	1.7	1.67	0.78–3.55	0.18
>249	1,094	1.7	1.67	0.79–3.52	0.18
Number of significant lesions (70%)					
0/1	992	1.2	1.0	Reference	—
2	739	1.1	0.89	0.36–2.20	0.81
3	537	0.9	0.77	0.27–2.19	0.62
4	341	1.5	1.21	0.42–3.47	0.72
≥5	570	3.2	2.66	1.27–5.57	0.009
Number of lesions attempted					
1	2,400	1.3	1.0	Reference	—
2	650	2.1	1.68	0.89–3.18	0.11
≥3	129	2.3	1.82	0.55–6.03	0.33
Stent used					
No	165	2.4	1.68	0.59–4.72	0.33
Yes	3,014	1.5	1.0	Reference	—
Contrast media type*					
Nonionic low osmolar	1,749	1.4	1.0	Reference	—
Nonionic iso-osmolar	943	1.6	1.14	0.60–2.17	0.68
Ionic high osmolar	67	0	n/a	n/a	n/a
Ionic low osmolar	304	2.3	1.67	0.72–3.87	0.23

*Patients given more than one type of contrast media have been excluded (n = 11).
MI = myocardial infarction; PCI = percutaneous coronary intervention.

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Table 3 Univariate Association of In-Hospital Outcomes With an Early Abnormal Creatinine Increase After Percutaneous Coronary Intervention

Factor	Number of Patients	Incidence (%)	Odds Ratio	95% Confidence Interval	p Value
Total angiographic success					
No	144	5.6	4.40	2.02–9.57	<0.001
Yes	3,029	1.3	1.0	Reference	—
Procedural success					
No	98	10.2	9.08	4.38–18.81	<0.001
Yes	3,075	1.2	1.0	Reference	—
Bleeding requiring transfusion					
No	3,125	1.3	1.0	Reference	—
Yes	54	13.0	11.20	4.78–26.26	<0.001
Death					
No	3,153	1.3	1.0	Reference	—
Yes	26	26.9	27.97	11.15–70.16	<0.001
Death or myocardial infarction					
No	3,082	1.3	1.0	Reference	—
Yes	97	9.3	7.98	3.75–16.98	<0.001
Stroke					
No	3,167	1.5	1.0	Reference	—
Yes	10	10.0	7.38	0.92–59.39	0.06
MACE					
No	3,063	1.3	1.0	Reference	—
Yes	116	7.8	6.52	3.08–13.82	<0.001

MACE = major adverse clinical event.

early abnormal increase in creatinine (Table 4). Notably, the total volume of contrast was not retained in the final model.

Discussion

In this report we show the predictive utility of the ratio of the volume of contrast media administered to the estimated creatinine clearance in assessing the risk of an abnormal early post-PCI increase in serum creatinine. Because V/CrCl corresponds closely to the area under the blood contrast media concentration versus time curve, this index should more closely predict the safety profile of contrast media, particularly with respect to the risk of CAN, than the absolute volume of contrast alone.

The literature on the subject of CAN is extensive and has been the subject of numerous recent comprehensive reviews (3,23–27). Several studies have sought to establish a relationship between the total volume of contrast media administered, baseline renal function, and risk of CAN after

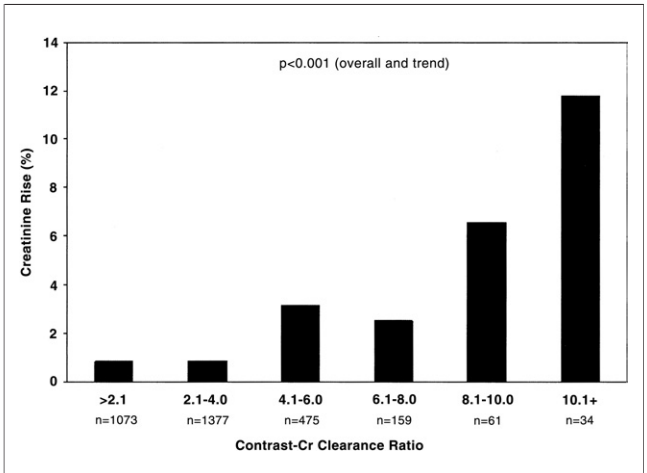

Figure 1 Relationship Between V/CrCl Ratio and Early Creatinine Increase

The association between ratio of the volume of contrast media to the creatinine clearance (V/CrCl) and the percentage of patients with an early abnormal increase in creatinine after percutaneous coronary intervention (PCI) was highly significant ($p < 0.001$ overall and for trend).

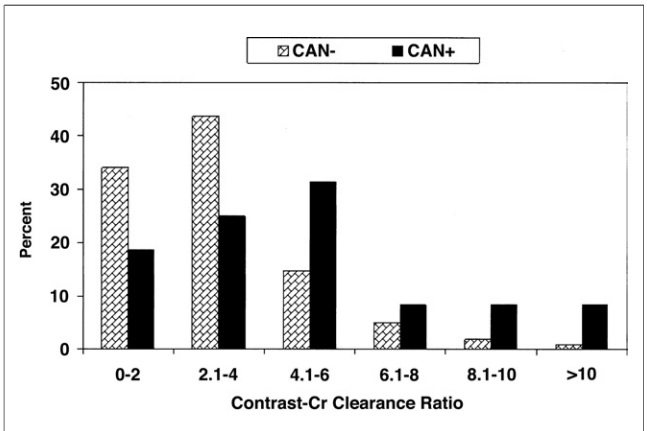

Figure 2 Distribution of V/CrCl Ratio in Current Study

The distributions of ratio of the volume of contrast media to the creatinine clearance (V/CrCl) values in patients with and without an early abnormal increase in creatinine were significantly different ($p < 0.001$). CAN = contrast media-associated nephrotoxicity.

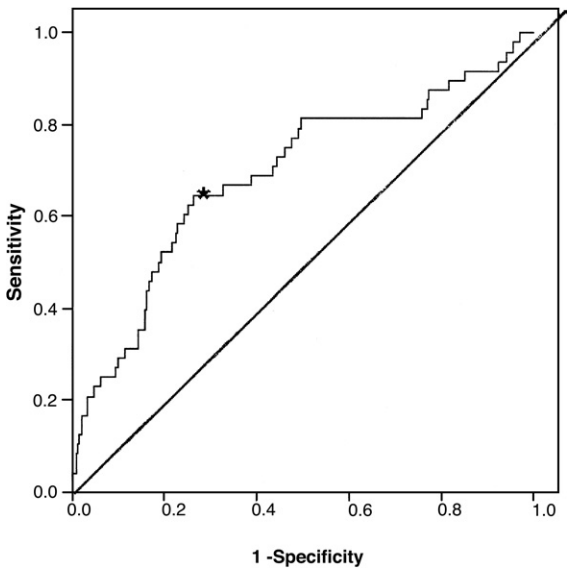

Figure 3 Receiver-Operator Characteristics Curve

Receiver-operator characteristics analysis indicated an optimum cutoff value for ratio of the volume of contrast media to the creatinine clearance (V/CrCl) of 3.7 **(*)**. The C-statistic was 0.69.

angiography. Contrast volume/CrCl was used in a retrospective analysis of 152 patients with chronic kidney disease (defined as a baseline creatinine >2.0 mg/dl) and was found to be predictive of CAN (defined as an increase in creatinine of 1.0 mg/dl) at a cutoff value of 6.0 (28). This cutoff was then used prospectively in 250 consecutive patients (creatinine of 0.3 to 5.8 mg/dl) and found to have a sensitivity of 79% and specificity of 97% for predicting CAN (28). These data are not strictly comparable with those reported herein because of differences in the number of patients studied, the number with chronic kidney disease, and the definition and overall incidence of CAN.

A contrast volume limit of 5 ml/kg divided by serum creatinine has been proposed as a way to predict CAN in patients receiving contrast media (29). This was validated in 115 patients with chronic kidney disease (Cr >1.8 mg/dl) undergoing angiography. Patients who received >5 ml/kg/serum creatinine had a higher incidence of CAN. This formula was applied retrospectively in 16,592 patients undergoing cardiac catheterization to determine its utility in predicting the risk of postprocedural dialysis. Patients who received a volume of contrast in excess of 5 ml/kg/serum creatinine were 6-fold more likely to develop nephropathy requiring dialysis (30).

In our study of 3,179 consecutive unselected patients undergoing PCI, we found that a V/CrCl >3.7 predicted the patient at risk for an abnormal early postprocedural increase in creatinine. In contrast to the aforementioned studies, we included a broader spectrum of patients and used a more practical criterion for CAN—an early, abnormal increase in creatinine. Although the true incidence of the traditionally defined CAN (2,3) is likely underestimated in our study because of the failure to obtain sufficient samples beyond 24 h, our results are relevant to those patients for whom the detection of an early increase in postprocedural creatinine may be meaningful (31). Such evidence of renal vulnerability to the effects of contrast media are useful for risk stratification. Furthermore, real-world clinical practice often precludes observing the majority of patients beyond 24 h. Despite the likely underestimation of the incidence of CAN without systematic 48- and 72-h sampling, our data regarding the value of V/CrCl as a predictor of an early postprocedural increase in creatinine remain valid. In this sample we were also able to confirm the previously described association between an abnormal post-PCI creatinine increase and adverse in-hospital outcomes (9) despite the overall low risk of the present population. Additional studies of the utility of this ratio in populations with more prevalent underlying kidney disease undergoing angiography and/or PCI and with more extended creatinine determinations would be informative.

The relationship posited herein between contrast volume, renal exposure, and the risk of CAN does not take into account the many unpredictable hemodynamic and rheologic disturbances during PCI. Previous studies, as well as the present

Table 4 Multivariable Association Between an Early Abnormal Increase in Creatinine Level After PCI and V/CrCl Ratio

Variable	Odds Ratio	95% Confidence Interval	p Value
Volume/CrCl ratio ≥3.7	3.84	2.01–7.34	<0.001
Age >65 yrs	1.71	0.85–3.43	0.13
Black (vs. other races)	2.26	1.17–4.36	0.015
Attempted high-risk lesion without collaterals	4.26	1.01–18.00	0.049
Diabetes mellitus	1.43	0.77–2.65	0.26
History of congestive heart failure	2.55	1.27–5.09	0.008
Emergent PCI	3.92	2.00–7.66	<0.001
Chronic kidney disease	2.49	1.19–5.21	0.016

Variables considered but not included in the final model: gender, height, weight, body mass index, prior PCI, prior coronary bypass surgery, prior myocardial infarction, hypertension, dyslipidemia, smoking, vessel disease, reason for revascularization (i.e., stable angina, unstable angina, acute myocardial infarction), cardiogenic shock, attempted lesion containing thrombus, attempted totally occluded lesion, attempted lesion located in a vein graft, attempted lesion located in a bifurcation, attempted lesion supplying collateral vessels, attempted torturous lesion, attempted lesion located in an ostial location, attempted lesion with calcium, number of significant lesions, number of lesions attempted, contrast media volume, history of peripheral vascular disease, stent use, history of cerebrovascular disease, and history of pulmonary disease.

PCI = percutaneous coronary intervention; V/CrCl = volume of contrast media to the creatinine clearance.

study, have identified numerous clinical, demographic, and procedural factors that are significantly associated with CAN after PCI (32,33). That V/CrCl remained independently associated with the risk of an early postprocedural creatinine increase after adjustment for these important confounders (Table 4) is supportive of our original hypothesis.

This study was not intended to examine the relationship between the type of contrast media and the risk of CAN. The inability to identify an association between these variables is the result of a combination of factors: nonrandom assignment of contrast media, operator bias in the choice of contrast media, and type II error attribuable to the low overall event rate.

Although V/CrCl is useful in retrospective analyses of the relationship between contrast volume and subsequent renal injury, the cut point of 3.7 may be a useful tool in determining the amount of contrast volume that is likely to result in an early abnormal increase in creatinine. Thus, multiplying a patient's estimated CrCl by 3.7 would give an estimate of the maximum amount of contrast for a given procedure, above which the likelihood of developing renal injury would be concerning.

In summary, we have shown that V/CrCl is a useful and independent predictor of an early increase in postprocedural serum creatinine in unselected patients undergoing PCI. This index may be applied prospectively to calculate the maximum volume of contrast media that can be given without significantly increasing the risk of CAN.

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