BRIEF REPORT

Creatinine Clearance and Contrast Nephropathy in Patients With Normal Creatinine Levels

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The main risk factor for contrast nephropathy is the presence of poor renal function. Plasma creatinine level is not a reliable measure of renal function as its value could lie within the normal range despite the presence of significant nephropathy. The purpose of this study was to evaluate the creatinine clearance rate as a predictor of contrast nephropathy in patients with a normal plasma creatinine level. The study included 273 consecutive patients with non-ST elevation acute coronary syndrome (NSTEACS) and a normal plasma creatinine level at admission who underwent coronary angiography. Patients who developed contrast nephropathy had a lower creatinine clearance rate at admission (66.3 mL/min vs 83.4 mL/min; *P*<.001). A creatinine clearance rate <80 mL/min had a sensitivity of 81% for predicting contrast nephropathy. Creatinine clearance should be measured routinely in patients with NSTEACS who are scheduled for coronary angiography.

Key words: *Creatinine clearance. Coronary angiography. Contrast nephropathy.*

Aclaramiento de creatinina y nefropatía por contraste en pacientes con creatinina normal

El principal factor de riesgo de nefropatía por contraste (NC) es la presencia de una función renal deteriorada. La creatinina plasmática (Cp) es una medida poco exacta de la función renal y puede ser normal en presencia de nefropatía significativa. El objetivo del estudio es evaluar el valor del aclaramiento de creatinina (ACr) como predictor de NC en pacientes con Cp normal. Se incluyó a 273 pacientes consecutivos con síndrome coronario agudo sin elevación del segmento ST (SCASEST), con Cp normal en el momento ingreso y en los que se realizó una coronariografía. El ACr fue significativamente menor en el grupo de pacientes que presentaron NC (66,3 frente a 83,4 ml/min: p < 0,001). Un ACr < 80 ml/min presentó una sensibilidad de 81% para predecir el desarrollo de NC. El ACr se debería obtener de manera sistemática en pacientes con SCASEST.

Palabras clave: *Aclaramiento de creatinina. Coronariografía. Nefropatía por contraste.*

INTRODUCTION

Contrast-induced nephropathy (CN) is the third most common cause of acute renal failure in hospitalized patients, only exceeded by hypotension and surgery. Far from being a trivial problem, CN is associated with prolongation of hospital stay and increased in-hospital and long-term morbidity and mortality.[1-3] Currently, the most widely accepted definition of CN is an increase in plasma creatinine (PCr) concentration ≥0.5 mg/dL or >25% with respect to the baseline value over the days following administration of radiocontrast material.[1-5]

The incidence of CN in patients undergoing cardiac catheterization ranges from 2% to 50%, depending on the definition of CN used and the patients' risk factors.[2-5] The main risk factor for this condition is altered renal function at baseline. Other factors related to the development of CN are diabetes, volume depletion, anemia, heart failure, hypotension, use of an intra-aortic counterpulsation balloon, and the volume and type of contrast agent used (those with low osmolarity are associated with a lower incidence of CN).[5,6]

Proper stratification of the risk of presenting CN before catheterization allows establishment of prophylactic

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measures in high-risk patients.[3,4] The prophylactic strategies supported by the highest level of scientific evidence are hydration[7] and the use of contrast material having a low osmolarity.[5,6] Favorable results, although less consistent, have been obtained with N-acetylcysteine,[8,9] bicarbonate,[10,11] and hemofiltration.[12] In addition, potentially nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor antagonists, diuretics, and metformin) should be discontinued for 24 to 48 h.[13]

The main predictor of contrast nephropathy is altered renal function at baseline. Plasma creatinine analysis is an indirect, imprecise measure of renal function that is influenced by several factors such as the patient's age, sex, and weight. This parameter can be within normal levels even when there is substantial nephropathy.[13] Creatinine clearance (CCr) is a more reliable indicator of the patient's glomerular filtration rate[2] and can be obtained by analysis of 24-hour urine or by calculation with formulas that offer an approximation. The most commonly used are the Cockroft-Gault and the Modification of Diet in Renal Disease (MDRD) formulas.[14]

The aim of this study was to assess the CCr value as a predictor of the development of CN in patients with normal plasma creatinine levels, in order to provide the possibility to initiate prophylactic measures and thereby decrease the incidence of CN in this subgroup of patients, which is considered a priori to be at low risk.

METHODS

The study was undertaken in 382 consecutive patients admitted to our unit for non-ST-elevation acute coronary syndrome (NSTEACS) during 2005. The inclusion criteria were baseline PCr value within the normal limit (≤1.3 mg/dL) and cardiac catheterization during hospitalization. Fifty-one patients with a baseline PCr concentration >1.3 mg/dL and 58 other patients in whom cardiac catheterization was not ultimately performed were excluded. A final total of 273 patients were included. The CCr value was calculated at the time of admittance using the Cockroft-Gault formula:

$$CCr=(140–age)\times weight(\times 0.85 \text{ in women})/Cr\times 72$$

The development of CN was investigated, as defined by a PCr elevation ≥0.5 mg/dL or >25% with respect to the baseline value in the days after cardiac catheterization.[1-5] Following the invasive procedure, all patients received protocolled antithrombotic therapy combined with acetylsalicylic acid, heparin, and glycoprotein 2b/3a inhibitor, in addition to clopidogrel. Unless there were contraindications, all patients received β-blockers and simvastatin. Angiotensin-converting enzyme inhibitors were given to all patients with diabetes, ventricular dysfunction, or anterior infarction and were generally considered in all cases except those with contraindications or hypotension. Diuretics were administered in patients with heart failure or oliguric renal failure only when considered appropriate. Patients presenting pain were given nitroglycerin for the first 24 h. The type of contrast used in all patients was iopamidol, a monomeric, nonionic, hypo-osmolar contrast medium.

Statistical Analysis

Quantitative variables are expressed as the mean (standard deviation) and qualitative variables as the absolute value and percentage. Student *t* test was used to analyze associations between a dichotomous qualitative variable and a quantitative variable and the χ^2 test was used for 2 qualitative variables. The overall diagnostic efficacy of PCr and CCr as predictors of CN was assessed by constructing receiver operating characteristic (ROC) curves and calculating the respective areas under the curve. Multivariate logistic regression analysis was performed, excluding the variables age and sex because they are included in the CCr formula. A *P* value less than .05 was considered significant. SPSS 12.0 was used for the statistical analysis.

RESULTS

A total of 63 (23%) patients presented CN, and 6 of them developed oliguric renal failure. In all 6 patients, the onset of oliguria was early and none of them presented eosinophilia or other evidence indicative of atheroembolism. Among these 6 patients, 1 required hemodialysis, 4 improved with diuretics, and 1 improved with rehydration therapy. The CCr value at the time of admission was significantly lower in the group of patients who developed CN (66.3 vs 83.4 mL/min; *P*<.001). Other variables that correlated with the development of CN were age (*P*<.001), female gender (*P*=.002), diabetes (*P*=.001), hypertension (*P*=.019), hemoglobin (*P*<.001), and Killip class (*P*<.001). Nevertheless, there was no correlation with baseline PCr (*P*=.54) or undergoing angioplasty (*P*=.46). Smoking was less frequent in the group that presented CN. Results are shown in Table. The ROC curve (Figure 1) presented an area under the curve of 0.71 for CCr and 0.46 for baseline PCr. Because the prophylactic measures for potential use are quite noninvasive, we sought a very sensitive cut-off value on the ROC curve to predict the development of CN. A CCr value <80 mL/min presented a sensitivity of 81% and a specificity of 50% for predicting the development of CN. A total of 62 patients (22%) presented a CCr value <60. The CCr was classified by intervals and the incidence of CN was calculated in each of them. The incidence rose from less than 10% in patients with a CCr ≥80 mL/min to 70% in the group with a rate of 20 to 40 mL/min (Figure 2). In the multivariate analysis, the variables that proved to

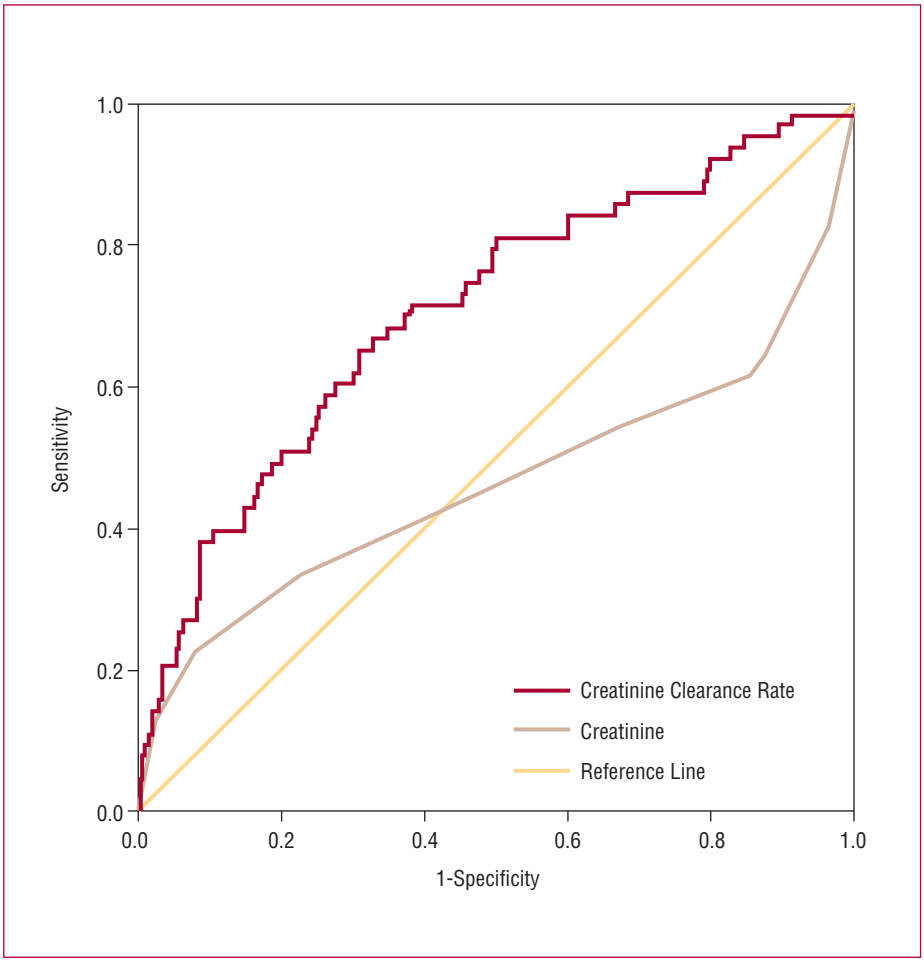

Figure 1. ROC curve for creatinine and creatinine clearance rate to predict contrast-induced nephropathy.

be independent risk factors for the development of CN were Killip class (odds ratio [OR], 14.7; 95% confidence interval [CI], 3.5-62.1; *P*<.001), hemoglobin (OR, 0.64; 95% CI, 0.51-0.80; *P*<.001), and CCr (OR, 0.97; 95% CI, 0.95-0.98; *P*<.001). Separate analysis of the variables contained in the Cockroft-Gault formula showed that age was an independent predictor of CN (OR, 1.10; 95% CI, 1.06-1.15; *P*<.001), in addition to Killip class (OR, 6.11; 95% CI, 2.16-17.26; *P*=.001) and hemoglobin (OR, 0.63; 95% CI, 0.51-0.79; *P*<.001).

Distribution of the Variables in the Study Groups*

	CN (n=63)	No CN (n=210)	*P*
Mean age	74.4 (9.1)	63.2 (11.7)	<.001
Male sex	4 (53.9%)	159 (71.9%)	.002
Diabetes	29 (46.1%)	52 (31.8%)	.001
Smoker	4 (38%)	111 (52.2%)	.045
Hypercholesterolemia	35 (55.5%)	107 (51.7%)	.56
HT	46 (73%)	118 (55.8%)	.019
Hemoglobin	12.3 (1.7)	13.9 (1.4)	<.001
Baseline PCr	0.98 (0.24)	0.96 (0.15)	.54
Baseline CCr	66.3 (26.6)	83.4 (24.2)	<.001
Killip ≥II	16 (25.3%)	3 (1.4%)	<.001
PTCA	33 (52%)	122 (58.3%)	.46
IABC	1 (0.15%)	2 (0.1%)	.56

*CCr indicates creatinine clearance; HT, hypertension; IABC, intra-aortic balloon counterpulsation; PCr, plasma creatinine; PTCA, percutaneous transluminal coronary angioplasty.

DISCUSSION

The creatinine clearance rate provides a reliable estimation of the glomerular filtration status and allows identification of patients at an elevated risk of presenting CN, although their PCr levels are within the normal limits. These patients would be eligible to receive renal prophylaxis measures before undergoing cardiac catheterization. The high prevalence in our series (22%) of deteriorated renal function, defined as CCr <60, in patients with normal PCr concentrations is worthy of note.

It is well-recognized that PCr analysis is an inaccurate means to estimate a patient's renal function. Nonetheless, in daily clinical practice, patients with normal creatinine concentrations are considered to be at low risk and do not usually receive renal prophylaxis before

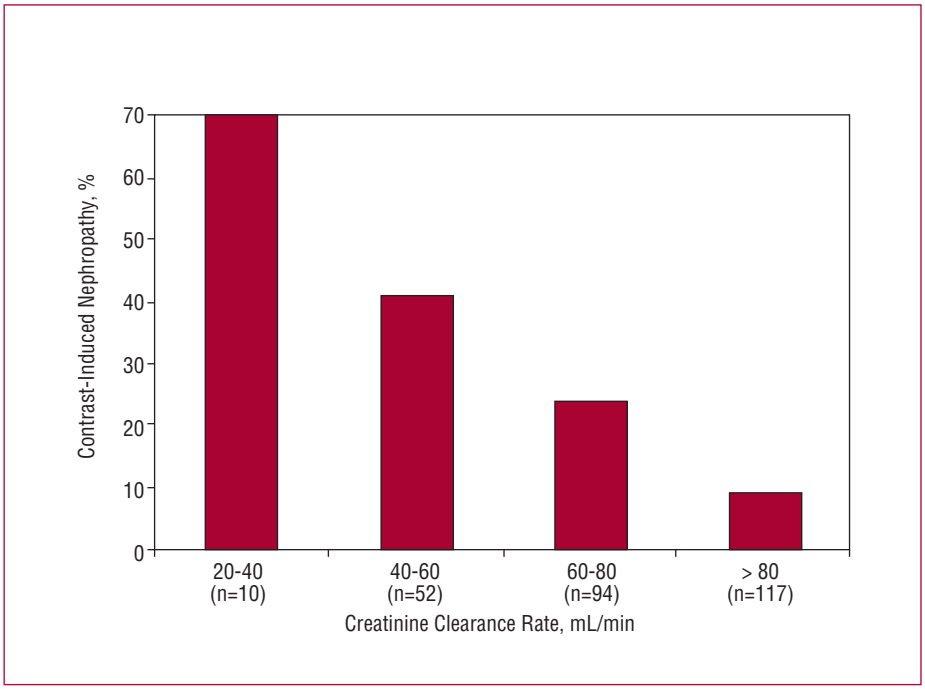

Figure 2. Incidence of contrast-induced nephropathy according to creatinine clearance values.

catheterization. It may be beneficial to perform CCr analysis in all patients about to undergoing coronary angiography. In patients with acute coronary syndrome, the need to perform early catheterization impedes CCr measurement in 24-hour urine samples. In these patients, estimation of the CCr with the use of a formula (Cockroft-Gault or MDRD) is of interest, since it offers a fast approximation of the patient's true renal function and allows early establishment of measures for renal prophylaxis before catheterization. It has been reported that low-risk patients also benefit from renal prophylaxis before undergoing catheterization.[9] Thus, it is likely that future trends in this line will lead to the application of routine prophylactic measures in all patients, not only those at high risk.

The incidence of CN in the present study was relatively high (23%) as compared to values obtained in previous studies. This may be because the risk profile of the study population was not low: mean age of the patients was 66 years and 30% had diabetes. When only the classical criteria were applied (creatinine increase >0.5 mg/dL), which are more restrictive, the incidence of CN decreased to 10%. The criterion of a creatinine increase greater than >25% of the baseline value, which is more sensitive, diagnosed small PCr elevations as CN. One might assume that such small increases are irrelevant, but they have been associated with prolongation of the hospital stay and increased in-hospital and long-term morbidity and mortality.[1,2]

The fact that the baseline PCr level did not correlate with the development of CN in patients with creatinine values <1.3 mg/dL may be surprising. The likely explanation is that the poor correlation between PCr and the glomerular filtration rate is enhanced when PCr values are within normal limits.[15]

Limitations

The main limitations of this study are those inherent to retrospective analyses. Certain data that could have been of interest, such as urine sodium levels and volume of contrast administered to each patient, were not available. In addition, other causes of renal failure (dehydration, drugs, atheroembolism, and the infarct, itself) could not be completely ruled out. Lastly, estimation of the CCr by means of a formula that includes other risk factors, such as age and sex, decreases the value of the multivariate analysis. Future studies measuring the CCr in 24-hour urine samples will clarify this question.

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