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Changing Trends in Incidence and Predictors of Radiographic Contrast Nephropathy After Percutaneous Coronary Intervention With Use of *Fenoldopam*

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O f the several agents that have been studied in the prevention of radiographic contrast nephropathy (RCN), saline hydration, use of nonionic dye, and N-acetylcysteine have been promising.[1–11] No agent, however, has been shown to be effective in diabetics, especially those with baseline serum creatinine ≥2.0 mg/dl. Bakris et al[12] showed that selective dopamine-1 receptor agonist fenoldopam protects against contrast-mediated reduction in renal blood flow compared with Schering 23390, a dopamine-1 receptor antagonist. Although fenoldopam has been shown to be a "reno-protective" agent in the setting of renal ischemic injury during percutaneous coronary intervention (PCI),[13] its role in high-risk patients with diabetes mellitus and chronic renal insufficiency has not been studied. The present study evaluates the incidence and predictors of RCN after PCI with use of fenoldopam in high-risk patients.

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All patients undergoing PCI from November 1999 to June 2001 at Mount Sinai Hospital, who had base-line serum creatinine ≥1.5 mg/dl before initiation of hydration, were retrospectively analyzed. Patients with acute myocardial infarction, cardiogenic shock, decompensated congestive heart failure, systolic blood pressure <90 mm Hg, patients on dialysis, and patients only undergoing diagnostic cardiac catheterization or peripheral vascular angiography were excluded. In all cases, the low osmolar nonionic contrast agent Ioversol (Optiray, Mallinckrodt Inc., St Louis, Missouri) was administered. Fenoldopam was given to 260 consecutive patients with baseline serum creatinine ≥1.5 mg/dl.

Baseline serum creatinine, blood urea nitrogen, and routine serum chemistry were obtained before hydration. All patients received 0.45% of normal saline at 1.0 ml/kg/hour for 6 to 12 hours before their procedure, except patients with compensated heart failure or left ventricular ejection fraction <30% in whom the saline infusion rate was reduced to 0.5 ml/kg/hour. Intravenous fenoldopam was started 15 to 20 minutes before contrast injection at a rate of 0.1 μg/kg/min, and was continued during PCI if the patient's blood pressure was stable. Procedural hemodynamics, procedure type, and the contrast agent amount used were recorded in case report forms. Fenoldopam was discontinued if systolic blood pressure decreased to <90 mm Hg despite reducing the dose to one half or one third. After our experience with the first 24 patients and observing significant hypotension in 4 patients

TABLE 1 Baseline Clinical Characteristics and Results in the Fenoldopam Group

Variables	All Patients (n = 260)	Diabetics (n = 143)	Nondiabetics (n = 117)	p Value
Age (yrs)	71 ± 12	69 ± 12	73 ± 12	0.006
Men	73%	66%	81%	0.01
Systemic hypertension	92%	95%	88%	0.03
Peripheral vascular disease	25%	28%	22%	0.28
Left ventricular ejection fraction (%)	40 ± 21	38.2 ± 22	42.8 ± 21	0.05
ACE inhibitors	56%	62%	50%	0.49
Contrast load (ml)	142 ± 59	150 ± 58	136 ± 61	0.06
Baseline serum creatinine (mg/dl)	2.08 ± 0.71	2.15 ± 0.74	2.01 ± 0.67	0.09
Peak serum creatinine (mg/dl)	2.01 ± 0.89	2.07 ± 0.95	1.92 ± 0.82	0.34
Change in baseline serum creatinine				
Increase >25%	3.8%	2.8%	5.1%	0.43
Increase or decrease ≤25%	87.3%	88.8%	85.5%	0.64
Decrease >25%	8.8%	8.4%	9.4%	0.62
Patients requiring dialysis	0.77%	0.70%	0.85%	0.55
Postprocedure LOS (days)	2.1 ± 3.0	2.1 ± 3.1	2.1 ± 3.0	0.92

LOS = length of stay.

TABLE 2 Baseline Clinical Characteristics and Results in the High-Risk Versus Low-Risk Groups

Variables	High Risk (n = 73)	Low Risk (n = 187)	p Value
Age (yrs)	68 ± 13	72 ± 11	0.05
Men	63%	77%	0.02
Diabetes mellitus	100%	37%	<0.0001
Systemic hypertension	96%	90%	0.16
Peripheral vascular disease	29%	24%	0.48
Left ventricular ejection fraction (%)	33 ± 22	43 ± 21	<0.0001
ACE inhibitors	53%	57%	0.81
Contrast load (ml)	124 ± 61	150 ± 58	0.0001
Baseline serum creatinine (mg/dl)	2.6 ± 0.7	1.8 ± 0.6	<0.0001
Peak serum creatinine (mg/dl)	2.6 ± 1.0	1.8 ± 0.7	<0.0001
Change in baseline serum creatinine			
Increase >25%	4.1%	3.7%	0.89
Increase or decrease ≤25%	89.0%	86.6%	0.38
Decrease >25%	6.8%	9.6%	0.42
Patients requiring dialysis	1.37%	0.53%	0.22
Postprocedure LOS (days)	2.5 ± 3.2	1.9 ± 3.0	0.22

Abbreviation as in Table 1.

with an initial fixed fenoldopam dose of 0.1 $\mu g/kg/min$, the dose of fenoldopam was gradually titrated in patients with borderline systolic blood pressure (90 to 120 mm Hg), compensated heart failure, or left ventricular ejection fraction <30%, starting from 0.03 $\mu g/kg/min$ to a maximum of 0.1 $\mu g/kg/min$ if the blood pressure was stable for 15 minutes on the lower dose. With gradual dose titration, discontinuation of fenoldopam for hypotension was rarely required. Hydration with 0.45% normal saline was maintained during and after the procedure for 10 to 12 hours. Fenoldopam infusion was continued for 6 hours after the procedure. Urine output was closely monitored to adjust the intravenous fluid replacement. Serum creatinine, blood urea nitrogen, and electrolytes levels were obtained at 24 and 48 to 72 hours after PCI and thereafter if still rising.

All interventions were performed using conventional techniques and the selection of a particular device was left at the discretion of the operator. The following devices were used for interventions: stent (75%), Rotablator (7%), Rota + stent (13%), AngioJet + stent (5%).

All patients were monitored for major ischemic complications (Q-wave myocardial infarction, emergent bypass surgery, or procedure-related death), periprocedural creatine kinase-MB elevation, recurrent chest pain, heart failure, arrhythmia (atrial or ventricular), electrocardiographic changes, acute or subacute closure, and for the need to repeat catheterization and intervention. Patients with rising serum creatinine levels were monitored in the hospital until serum creatinine levels started decreasing with or without dialysis. All patients who received RCN had renal consultation for subsequent workup and management.

RCN was defined as an increase in serum creatinine of >25% from baseline at 48 to 72 hours after PCI or an absolute increase in serum creatinine of >0.5 mg/dl. *No change in serum creatinine* was defined as a ≤25% increase or decrease in peak creatinine from baseline. *Contrast volume* was calculated by subtracting the volume remaining after PCI from the initial known contrast volume. *"High-risk"* patients were considered those with diabetes mellitus and baseline serum creatinine ≥2.0 mg/dl.

Data were entered in a Microsoft Excel database (Microsoft, Seattle, Washington) and transferred to the SAS.JMP 4 statistical program for analysis (SAS Institute, Cary, North Carolina). Groups were compared using chi-square analysis or Fisher's exact test for categorical variables and the Student's *t* test for continuous variables. A p value <0.05 was considered significant. Multivariate logistic regression analysis was used to determine predictors of renal function deterioration. Odds ratios and 95% confidence intervals are reported.

A total of 260 patients received fenoldopam and 254 patients completed the 6-hour drug infusion.
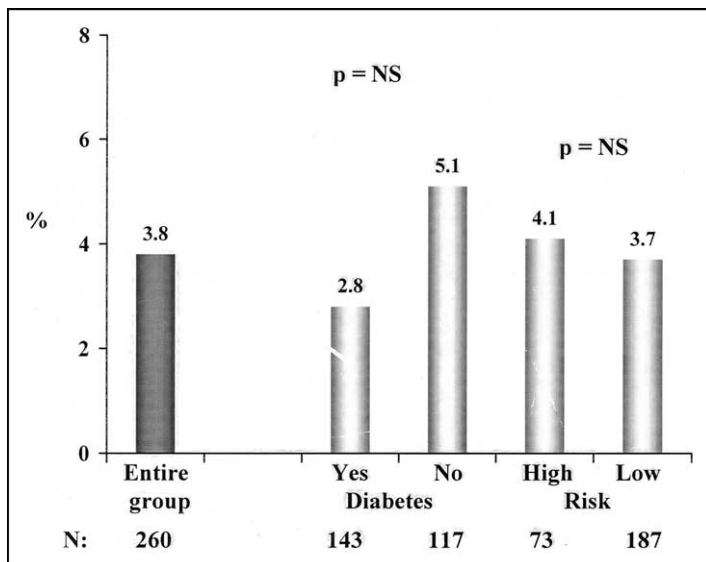
FIGURE 1. Incidence of radiographic contrast nephropathy in subsets of patients who underwent PCI and received fenoldopam.
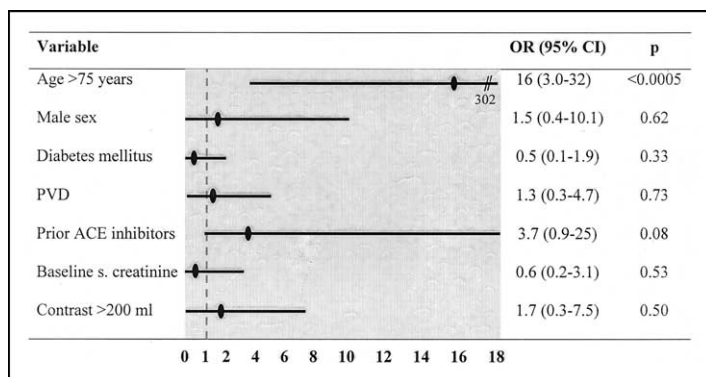

FIGURE 2. Predictors of RCN on multivariate analysis with fenoldopam use. ACE = angiotensin-converting enzyme; OR = odds ratio; PVD = peripheral vascular disease.

Baseline clinical characteristics of all patients are listed in Table 1. Most patients were aged >70 years (mean age 71 ± 12) and 73% were men; 55% were treated diabetics, 92% had history of systemic hypertension, and 25% had left ventricular ejection fraction <30%. Preprocedural medication included diuretics in 77% patients, calcium antagonists in 50%, angiotensin-converting enzyme (ACE) inhibitors in 56%, and β blockers in 38%. Compensated heart failure (New York Heart Association class <III) was present in 29%. The average contrast load for the entire group was 142 ± 59 ml.

The average baseline serum creatinine was 2.08 ± 0.71 mg/dl and peak creatinine 2.01 ± 0.89 mg/dl (p = NS). RCN was seen in 10 of 260 patients (3.8%). If the definition of >0.5 mg/dl absolute increase in serum creatinine is used, the incidence of RCN is 3.0%. Two patients required transient dialysis. Patients who developed RCN had an average age of 84 ± 7 versus 70 ± 12 years (p <0.0003), with peak creatinine levels of 3.7 ± 1.9 versus 1.9 ± 0.8 mg/dl (p <0.0001) and a similar contrast volume of 133 ± 65

versus 143 ± 60 ml (p = NS) when compared with patients who did not develop RCN.

The incidence of RCN (Table 2) was 2.8% in diabetics versus 5.1% in nondiabetics (p = NS). The average baseline serum creatinine was 2.15 ± 0.74 versus 2.01 ± 0.67 mg/dl, and peak creatinine was 2.07 ± 0.89 versus 1.92 ± 0.82 mg/dl in diabetics versus non-diabetics (p = NS). We analyzed the high-risk subgroup: patients with diabetes mellitus and baseline serum creatinine ≥2.0 mg/dl, who are the most vulnerable to develop RCN and observed that fenoldopam extends its renoprotective benefit in this high-risk subset (Figure 1). There were no major ischemic complications and 2 patients died in the hospital; both developed RCN and 1 required dialysis.

On univariate analysis, prior use of ACE inhibitors showed a trend toward an increase in postprocedure serum creatinine (p = 0.048). On multivariate analysis, age >75 years was a strong predictor for RCN (odds ratio 16, 95% confidence interval 3.0 to 32; p <0.0005). Previously established risk factors namely diabetes, contrast volume, and baseline serum creatinine did not predict RCN. Similarly, prior ACE inhibitor use was not a significant predictor of RCN in the multivariate model (Figure 2).

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The specific dopamine-1 receptor agonist[14] fenoldopam has been shown to be a safe and effective adjunctive drug for preventing RCN during angiography and PCI.[13,15,16] RCN is a potentially preventable condition, but is associated with high in-hospital mortality, morbidity, and poor long-term survival.[1,2] The most important finding in the present study is that fenoldopam significantly reduced the incidence of RCN in patients undergoing PCI compared with published data. Only Tepel et al[11] showed an incidence of RCN lower than that in our study, using acetylcysteine. In this study, a fixed dose of 75 ml of contrast was used in a noncoronary setting. Patients undergoing PCI usually have many comorbid conditions and may need a higher volume of contrast.

Hydration has been recommended as preventive measures in patients with chronic renal insufficiency undergoing angiography based on a study by Solomon et al[4] who showed that hydration with 0.45% normal saline significantly reduces the incidence of RCN compared with mannitol or furosemide. The addition of fenoldopam to preprocedure hydration may be a necessary supplement to protect the kidney during large contrast load during PCI. Also, Mathur et al[17] showed that there is a dose-dependent increment in renal blood flow with fenoldopam infusion, which may be more significant than the increase achieved by hydration alone. This can be substantiated by the fact that in our study, although statistically nonsignificant, diabetic

patients had a lower peak serum creatinine after receiving fenoldopam than nondiabetic patients.

The role of ACE inhibitors as potential risk for RCN has been controversial.[18] In our study, patients receiving ACE inhibitor therapy (56%) had a significant increase in serum creatinine after the procedure compared with patients without ACE inhibitors (p = 0.049). However, on multivariate analysis, prior ACE inhibitor therapy showed only a trend (p = 0.08) toward RCN development. Previously established important predictors such as hypertension and peripheral vascular disease were not predictors on univariate analysis. In the multivariate model, only advanced age was a significant independent predictor of RCN. Previously established risk factors such as chronic renal insufficiency, diabetes mellitus, and contrast volume did not predict RCN. This finding is different from previous studies in that fenoldopam appears to be more beneficial in patients with chronic renal insufficiency with or without diabetes, and this therefore changes the known predictors.

In conclusion, this study demonstrates that fenoldopam is especially renoprotective in patients with baseline serum creatinine ≥2.0 mg/dl, with or without diabetes, undergoing PCI along with hydration, by reducing the incidence of RCN to <4%. Also, previously established predictive risk factors of RCN are no longer significant after therapy with fenoldopam.

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Aortic Distensibility Is Increasing in Elite Athletes

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Physiolologic adaptations in an athlete's heart include increased left and right ventricular chamber size, increased left ventricular wall thickness and mass, and a decreased heart rate at rest.[1–3] It is known that static or isometric exercise is associated with concentric left ventricular hypertrophy, whereas endurance training or isotonic exercise is associated with eccentric left ventricular hypertrophy.[4] Because aortic elastic properties are important determinants of blood pressure and left ventricular function, this study was performed to assess the elastic properties of aorta in elite athletes.

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Thirty-three top-level male athletes (22 ± 4 years), all of whom were members of professional sports teams (14 runners, 10 wrestlers, 4 boxers, and 5 basketball players), and 14 age-matched healthy male controls (23 ± 1 years) were included in the study. The athletes had been competing for a mean of 7 ± 4 years; their mean training time was 12 ± 4 hours/week. Athletes who were off-training or experiencing a prolonged rest (>10 days) were excluded. All sub-