Managing the High-Risk Patient: Experience with Fenoldopam, a Selective Dopamine Receptor Agonist, in Prevention of Radiocontrast Nephropathy During Percutaneous Coronary Intervention

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Acute worsening of renal function due to contrast agents occurs in 15% to 40% of patients with baseline renal insufficiency undergoing percutaneous coronary intervention. Radiocontrast nephropathy is associated with increased morbidity, prolonged hospitalization, and higher in-hospital mortality. Our nonrandomized data suggest that in adequately hydrated patients, the dopamine-1 receptor agonist fenoldopam is a useful adjunct during PCI for prevention of RCN, reducing its incidence to less than 5%. This renoprotective effect of fenoldopam was more pronounced in diabetics, with moderate renal failure, in whom no agent has been shown so far to be beneficial. [Rev Cardiovasc Med. *2001;2(suppl 1):S19–S25*]

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Radiographic contrast nephropathy (RCN) is the third leading cause of hospital-acquired renal insufficiency[1] and contributes to morbidity, prolonged hospitalization, in-hospital mortality, increased health care costs, and permanent chronic end-stage renal disease.[2-6] About 5% to 10% of patients who develop RCN require transient dialysis, and fewer than 1% need long-term dialysis, but long-term survival is poor for all dialyzed patients.[2,4] RCN causes an asymptomatic increase of serum creatinine 24 to 72 hours after contrast

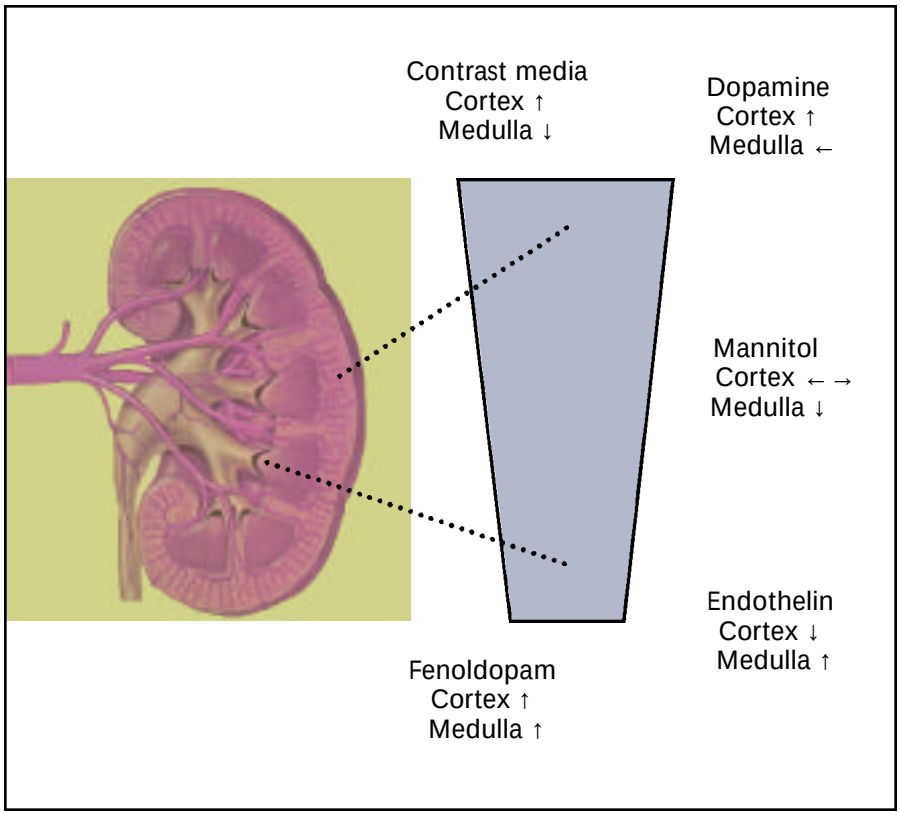


Figure 1. *Effects of various agents on regional renal blood flow.*

injection. Renal function remains depressed for few days to a few weeks (3 to 20 days) in most cases and then returns to baseline or near-baseline levels. Risk factors predisposing to RCN include renal insufficiency (baseline serum creatinine [BSCr] > 1.5 mg/dL), diabetes mellitus, dehydration, use of diuretics, use of a large volume of contrast, repeated exposure to contrast in less than 48 hours, congestive heart failure, advanced age, and hypertension.[4,5,7-11] Many studies have implicated diabetes mellitus as an independent risk factor for RCN.[4,7-9,11]

The mechanism of RCN is multifactorial. After contrast injection, there is an initial brief rise in blood flow followed by a prolonged fall, which lasts longer in patients with risk factors for RCN, especially after multiple contrast injections.[2] More importantly, contrast causes shunting of blood from renal medulla to cortex, causing medullary ischemia.[12]

Radiocontrast nephropathy is the third leading cause of hospital-acquired renal insufficiency.

Several trials have evaluated prophylactic measures for RCN prevention,[3,8-21] such as saline hydration, furosemide, mannitol, calcium blockers, atrial natriuretic peptide, aminophylline, N-acetylcysteine, and dopamine. However, the preventive efficacy of most of these agents has been inconclusive, except for saline hydration, as shown by Solomon et al.[13] Fenoldopam, an antihypertensive, is a selective dopamine-1 (DA_1) receptor agonist that increases renal blood flow by dilating both the cortical and the medullary renal vasculature, thereby counteracting contrast-induced medullary ischemia (Table 1, Figure 1). Bakris et al[19] showed that the DA_1 receptor agonist fenoldopam protects against contrast-mediated reduction in renal blood flow compared to Schering 23390, a DA_1 receptor antagonist.

Contrast causes shunting of blood from renal medulla to cortex, causing medullary ischemia.

Methods

Patients. A prospective study conducted from January 1999 to August 2000 at Mount Sinai Hospital included all patients undergoing PCI who had baseline serum creatinine concentrations greater than 1.5 mg/dL prior to initiation of hydration and who had one or more of the following risk factors: diabetes mellitus, compensated heart failure, age more than 70 years, or hypertension. Patients with acute myocardial infarction, cardiogenic shock, decompensated congestive heart failure, systolic blood pressure less than 90 mm Hg; patients on dialysis; and patients having only diagnostic cardiac catheterization or peripheral vascular angiography were excluded. In all cases, the low-osmolar nonionic contrast agent iohexol (Optiray, Mallinckrodt Inc., St Louis, MO) was used. Fenoldopam was used in 110 consecutive patients

Table 1
Adrenergic Receptor Agonism: Dopamine vs Fenoldopam

Receptor	Effects	Dopamine	Fenoldopam
DA_1	Peripheral vasodilation	+++	+++
	Renal: ↑ RBF, ↑ GFR ↑ diuresis	+++	+++
DA_2	Peripheral vasodilation	+++	–
	Renal: ↓ RBF, ↓ GFR ↓ diuresis	+++	–
α	Vasoconstriction	++	–
β_1	Inotropy, chronotropy	+++	–
β_2	Vasodilation	+	–

DA_1, dopaminergic-1; DA_2, dopaminergic-2; GFR, glomerular filtration rate; RBF, renal blood flow.

from November 1999 to August 2000. Patients undergoing PCI at Mount Sinai Hospital from January to October 1999 (before fenoldopam use), who had BSCr levels higher than 1.5 mg/dL prior to hydration and were not on dialysis served as historical controls, with similar inclusion and exclusion criteria used.

Protocol. All patients received 0.45% normal saline at 1.0 mL/kg/h for 10 to 12 hours prior to the procedure. Patients with compensated heart failure or left ventricular ejection fraction less than 30% received saline infusion at a rate reduced to 0.5 mL/kg/hr. Intravenous fenoldopam was started 15 to 20 minutes prior to contrast injection at a rate of 0.1 µg/kg/min and was continued during PCI if the patient's blood pressure was stable. In all patients, baseline serum creatinine and routine serum chemistry were obtained prior to hydration. Procedural hemodynamics and contrast agent amount used were recorded on case report forms. Fenoldopam was discontinued if systolic blood pressure decreased to less than 90 mm Hg despite reduction of the dose to one half or one third. Following our experience with the first 24 patients, among whom we observed significant hypotension in 4 patients with an initial fixed fenoldopam dose of 0.1 µg/kg/min, the dose of fenoldopam was gradually titrated in patients with borderline systolic blood pressure (90 to 120 mm Hg) or left ventricular ejection fraction less than 30%, starting from 0.03 µg/kg/min and reaching a maximum of 0.1 µg/kg/min if the blood pressure was stable for 15 min on the lower dose. 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. Serum creatinine and blood urea nitrogen levels were obtained at 24 and 48 to 72 hours after PCI and later if they were still rising.

All patients had serum electrolytes measured at 6 hours and serum creatinine measured at 24 and 48 hours after the procedure. After our initial experience with fenoldopam in the first 30 patients, during which no rise in serum creatinine was observed at 24 hours in the majority, patients in whom serum creatinine 24 hours after PCI remained lower than baseline were discharged home, and a follow-up serum creatinine was obtained on an outpatient basis 24 to 48 hours after discharge.

Definitions. Radiographic contrast nephropathy was defined as an increase in serum creatinine of more than 25% from baseline 48 to 72 hours after PCI or an absolute increase in serum creatinine of more than 0.5 mg/dL. No change in serum creatinine was defined as 25% or less increase or decrease in peak creatinine from baseline.

Statistical analysis. The data were entered in a Microsoft Excel database and transferred to the statistical program for analysis. Groups were compared using chi-square analysis or Fisher's exact test for the categorical variables and Student's *t* test for the continuous variables. A *P* value greater than .05 was considered significant.

Results

A total of 110 patients received fenoldopam, and 106 patients completed the 6-hour postprocedure drug infusion. The majority of patients were over age 70 (mean age 72 ± 12 years); 72% were male; 58% were treated diabetics; 91% had a history of hypertension; and 25% had a left ventricular ejection fraction lower than 30%. Preprocedural medication included diuretics in 77% of patients, calcium blockers in 50%, ACE inhibitors in 60%, and β-blockers in 38%. Compensated heart failure (class III or lower) was present in 21% and Canadian cardiovascular angina class III to IV in 40%. The average contrast load was 151 ± 67 mL.

The changes in the serum creatinine concentration are shown in Table 2. Average BSCr was 2.14 ± 0.72 mg/dL and peak creatinine 2.05 ± 0.86 mg/dL (*P* value not significant). Radiographic contrast nephropathy was seen in 5 of 110 patients (4.5%). In 88.2% of the patients (n = 97) there was no change in serum creatinine (increase or decrease of 25% or less of BSCr), and in 7.3% of patients (n = 8) peak creatinine decreased by less than 25% of the BSCr. If the definition of more than a 0.5 mg/dL absolute increase in serum creatinine is used, the incidence of RCN was 4.5%. No patients required dialysis. The average age of the patients who developed RCN in the fenoldopam group was 84 ± 5.6; that of patients who did not develop RCN was 72 ± 12 years ($P < .01$). Peak creatinine levels in the 2 groups were 3.2 ± 1.5 and 1.9 ± 0.7, respectively ($P < .001$); volume of contrast was similar (*P* value not significant). The postprocedure length of stay was 4.1 ± 3.4 days in the RCN group and 2.8 ± 2.5 days in the no-RCN group ($P = .07$).

Many studies have implicated diabetes mellitus as an independent risk factor for RCN.

In the control group, with similar baseline characteristics except for fewer diabetics and less use of ACE inhibitors (Table 3), mean baseline and peak serum creatinine levels were 2.22 ± 0.90 mg/dL and 3.32 ± 1.11 mg/dL, respectively. The incidence of RCN in the control group was 18.8% (n = 22) with saline hydration only and 26.2% in treated diabetics. Six (27.2%) of these 22 RCN patients required transient in-hospital dialysis, and only one required long-term permanent dialysis. In comparison with historical controls at our institution, patients receiving fenoldopam had a significantly lower ($P = .0009$) RCN incidence (4.5%), and none required dialysis (Figure 2).

Discussion

This study has demonstrated for the first time that the specific DA_1 receptor agonist fenoldopam is a safe and effective adjunctive drug for prevention of RCN during PCI. Radiocontrast nephropathy is a potentially preventable condition, but it is associated with high in-hospital mortality and morbidity and with poor long-term survival.[4] Among various suggested pathogenetic mechanisms of RCN, medullary ischemia due to shunting of blood to renal cortex after contrast injection seems to be the most important factor.

Fenoldopam is a specific DA_1 receptor agonist, which unlike dopamine lacks DA_2 and α-, β1-, and β2-adrenergic receptor activity (Table 1). Renal outcomes with dopamine infusion following contrast administration in humans have not been consistent,[3,14,15] mainly due to the nonspecific nature of stimulation of both dopaminergic receptors, DA_1 and DA_2, which have opposite actions.[17] Being selective for DA_1 receptor stimulation, fenoldopam enhances both cortical and medullary renal blood flow and increases glomerular filtration, producing natriuresis and diuresis.[18] Patients undergoing PCI typically receive a larger dose of

Main Points

- Radiocontrast nephropathy (RCN) contributes to morbidity, long hospital stays, in-hospital mortality, increased health care costs, and permanent chronic end-stage renal disease.
- Risk factors predisposing to RCN include renal insufficiency and diabetes mellitus.
- Saline hydration helps prevent PCI-associated RCN; adding fenoldopam to hydration can further reduce the incidence of RCN, even in patients with diabetes or renal insufficiency.
- In patients at risk for a hypotensive response to fenoldopam, titrating the infusion up from a lower starting dose can prevent such a reaction.

Table 2

Effect of Fenoldopam on Renal Function in the Study Group and in Relation to Diabetic Status

Variables	All patients (n = 110)	Diabetics (n = 64)	Nondiabetics (n = 46)
BSCr (mg/dL)	2.14 ± 0.72	2.20 ± 0.71	2.06 ± 0.73*
Peak serum creatinine (mg/dL)	2.05 ± 0.86	2.1 ± 0.8	1.9 ± 0.9*
Baseline BUN (mg/dL)	45 ± 12	43 ± 11	47 ± 9
Peak BUN (mg/dL)	50 ± 10	48 ± 9	52 ± 11
BSCr ↑ >25% (%)	4.5	3.5	6.2*
BSCr ↑ ≤25% or ↓ ≤25% (%)	88.2	87.0	86.1
↓ >25% BSCr (%)	7.3	9.5	7.7
Patients requiring dialysis	0	0	0
Postprocedure length of stay (d)	2.9 ± 2.5	3.2 ± 2.8	2.5 ± 2.0

*P > .1.
BSCr, baseline serum creatinine; BUN, blood urea nitrogen.

Table 3

Baseline Clinical Characteristics in the Fenoldopam Group vs the Control Group

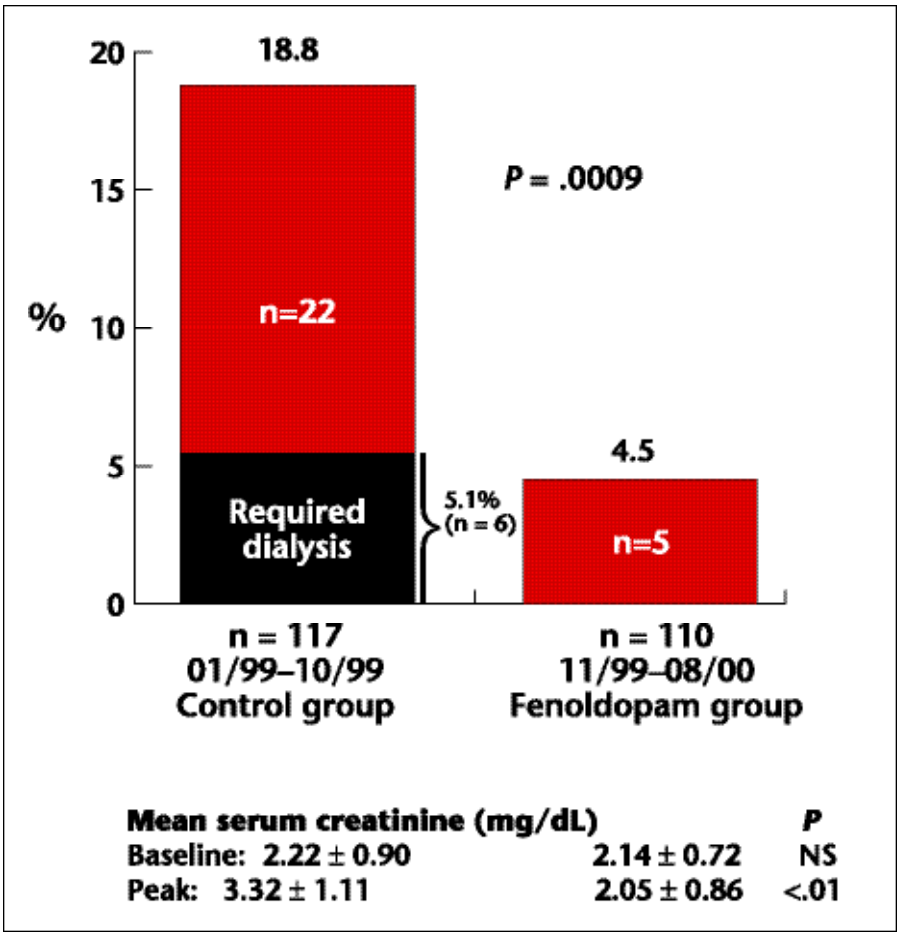
Variables	Fenoldopam group (n = 110)	Control group (n = 117)	*P* value
Age (y)	72 ± 12	72 ± 16	NS
Male (%)	72	70	NS
Weight (kg)	76.5 ± 13.6	73.3 ± 12.8	NS
Diabetes mellitus (%)	58	44	0.08
History of hypertension (%)	91	82	0.15
Angina class III-IV (%)	40	33	NS
LVEF <30% (%)	25	20	NS
Medication*			
Diuretics (%)	77	72	NS
Calcium blocker (%)	50	40	NS
ACE inhibitors (%)	60	44	0.04
β-blockers (%)	38		NS
Multivessel intervention (%)	10	4	0.04
Contrast load (mL)	151 ± 67	160 ± 61	NS
Procedural hypotension (%)	3.6	1.7	NS

*Many patients had more than one medication.
ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction.

Table 4
Steps for Prevention of RCN

- Optimize the general medical condition
- Administer saline (0.9 or 0.45 NS) hydration (0.3-1 mL/kg/h) for 6-12 h before and after PCI
- Hold furosemide in AM, ? hold ACE inhibitors
- Limit dye load (<100 mL)
- Stage repeated interventions at least 48 h apart
- Use nonionic, low-osmolar contrast agent
- Give N-acetylcysteine for 48 h periprocedurally
- Use fenoldopam—promising new agent!

Figure 2. *Incidence of RCN and mean baseline and peak serum creatinine in PCI patients with baseline renal dysfunction: historical controls vs patients who received fenoldopam treatment.*



contrast, in which case saline hydration alone may not be protective. The addition of fenoldopam during preprocedure hydration may be the necessary supplement to protect the kidney during the large contrast load used for PCI. Our experience also revealed that in some cases (eg, with baseline systolic blood pressure 110 mm Hg, LVEF less than 30%, compensated heart failure), fenoldopam infusion at the recommended dose of 0.1 µg/kg/min could be associated with significant hypotension. Therefore, in these cases, a lower starting dose of 0.03 µg/kg/min should be used, with gradual titration up to 0.1 µg/kg/min over 30 minutes. This approach has eliminated fenoldopam-induced hypotension in PCI patients.

Clinical implications. Our study has shown for the first time that fenoldopam can significantly reduce the incidence of RCN during PCI, even in patients with diabetes or renal insufficiency. Limitation of the contrast load, periprocedural hydration, and use of fenoldopam in high-risk patients undergoing PCI may be the key factors in prevention of RCN (Table 4). Fenoldopam's use may allow early discharge of patients with stable serum creatinine 24 hours postprocedure, with a planned outpatient creatinine measurement at 24 to 48 hours. These encouraging results need to be confirmed in a randomized trial. ■

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