

Use of a Dopamine-1 Receptor Agonist (Fenoldopam Mesylate) in High Risk
Interventional Radiology Patients to Ameliorate Contrast-Associated Nephropathy
Abbas A. Chamsuddin¹, M.D., Karen J. Kowalik², RN, MBA, Haraldur Bjarnason³, M.D.,
Charles A. Dietz², M.D. Michael S. Rosenberg², M.D., Maria D. Gomes², M.D., Colleen
M. McDermott² B.S., David W. Hunter², M.D.

¹ Cardiovascular and Interventional Radiology, Department of Radiology, University of
Tennessee, 865 Jefferson Ave., Suite 121C, Memphis, TN 38163

² Cardiovascular and Interventional Radiology, Department of Radiology, University of
Minnesota, MMC 292, 420 Delaware St. SE, Minneapolis, MN 55455

³ Cardiovascular and Interventional Radiology, Department of Radiology, Mayo Clinic,
St. Mary's Hospital Room 6-460, 1216 2nd St. SW, Rochester, MN 55902

Corresponding Author: David W. Hunter M.D.

Phone Number: (612)273-2826

Email: hunte001@umn.edu

Type of paper submitted: Major paper

Signature:

Fax number: (612)273-8495

**Use of a Dopamine-1 Receptor Agonist (Fenoldopam Mesylate) in High Risk
Interventional Radiology Patients to Ameliorate Contrast-Associated Nephropathy**

Abstract

Objective. The objective of our study was to evaluate the effects of fenoldopam (mesylate), a dopamine type 1A receptor agonist and a potent renal vasodilator that markedly increases renal blood flow, on the renal function of patients in interventional radiology who were receiving iodinated contrast material and who were felt to be at high risk of contrast-associated nephropathy.

Materials and Methods. We retrospectively reviewed the records of all patients who received fenoldopam to determine the acute and, when possible, the longer term effects on renal function.

Results. Twenty-nine patients were reviewed. The average serum creatinine value before contrast administration was 2.55 mg/dL (range, 1.3 mg/dL - 5.8 mg/dL). Twenty-four hours after contrast administration, serum creatinine was measured in 28 of the 29 patients. The serum creatinine values had decreased in 16 of 28 patients by an average of 0.5 mg/dL. In nine patients serum creatinine values had not changed. Of three of the patients in whom serum creatinine values increased, two appeared to be primarily due to problems not involving contrast material.

Conclusions. Use of fenoldopam at appropriate doses appears to offer high-risk patients a distinct chance of avoiding contrast-associated nephropathy. The extent and true nature of fenoldopam's effect in such patients requires a rigorous scientific trial, which is currently underway.

Introduction

Contrast-associated nephropathy is a potentially serious sequela of contrast media. This nephropathy may manifest as symptoms ranging from acute, irreversible renal failure to minor changes in tubular function tests. Contrast-associated nephropathy is an important cause of hospital-acquired renal insufficiency, and contributes to morbidity and mortality during hospitalization and to the incidence of chronic end-stage renal disease. Many drugs have been tested in an effort to decrease the incidence of contrast-associated nephropathy, none of which has ever been shown to have a definite clinical benefit until the recent study of n-acetylcysteine [1]. The only other treatment that offers any reduction in contrast associated nephropathy is pre-procedural hydration, and this regimen is only moderately effective [2, 3]. Reports in the surgical and intensive care literature [4-7] about fenoldopam, (Corlopam ®, Abbott Labs, Abbott Park, IL), an analogue of dopamine and a potent renal vasodilator which markedly augmented renal blood flow, indicated that it potentially demonstrated a beneficial effect on renal function in patients suffering from severe hypertension and a variety of medication related and ischemic insults. After analyzing these reports, we initiated a treatment plan for high-risk patients to attempt to ameliorate the negative effect of contrast on already compromised kidneys.

Materials and Methods

From January 19, 1999, to April 6, 2000, we treated 30 patients with fenoldopam. One received fenoldopam solely to control hypertension. Twenty-nine had conditions that placed them at high risk for contrast-associated nephropathy. This

group included diabetics with a serum creatinine value greater than or equal to 1.3 mg/dL, and non-diabetics with a serum creatinine value greater than or equal to 1.7 mg/dL. The patients were also selected because they were expected to require large contrast doses for complex interventional procedures, particularly renal arterial interventions and trans-jugular intrahepatic portosystemic shunts. This was, therefore, a highly selective, non-consecutive group of patients who were unequivocally felt to warrant a high-dose contrast study and in whom both the clinical status was appropriate and the logistical and nursing matters were able to be appropriately arranged. All patients were studied with a low osmolar, nonionic, monomeric contrast medium, Optiray 320®, (Mallinckrodt, St. Louis, MO).

Patients were started on a fenoldopam intravenous drip at a rate of 0.1 microgram/kg/min (0.1 g/kg/min) approximately two hours before contrast injection. The infusion rate was increased in increments of 0.1 g/kg/min every 20 minutes until a rate of 0.5 g/kg/min was reached. The patients' blood pressure was also checked every 20 minutes. An infusion rate increase was not made if there was a decrease in diastolic pressure of 20 mm Hg, systolic pressure of 30 mm Hg, or systolic pressure to a level < 110 mm Hg. If the systolic blood pressure dropped by 40 mm Hg or below 100 mm Hg, the infusion rate was either decreased to the next lower dose or stopped for ten minutes and restarted at the next lower dose. In hypertensive patients, a drop in systolic pressure up to 44% of the original value was expected. In some cases, this was a desired effect as anti-hypertensive medications had been stopped before the procedure.

The fenoldopam infusion was maintained at the highest achieved dose throughout the procedure and for a minimum of four hours after the termination of contrast injection. Serum creatinine values were obtained before the procedure and, whenever possible, daily, for two or three days after the procedure. After it became evident that most patients appeared to be deriving a distinct benefit from the treatment, permission was obtained from the Institutional Review Board of the hospital to review all of the patients' records for purposes of a retrospective review and plans for a prospective trial were initiated.

Results

Twenty-nine patients' records were evaluated. There were 18 males and 11 females (age range 33 to 85 years old). The factors that were felt to place them at high risk for contrast-associated nephropathy included chronic renal failure (20 of 29), diabetes (17 of 29), hypertension (16 of 29), renal artery stenosis (8 of 29), combined renal and hepatic dysfunction (7 of 29), and congestive heart failure (4 of 29). The procedures performed included peripheral diagnostic arteriography (6 of 29), trans-jugular intrahepatic portosystemic shunt (6 of 29), renal artery angioplasty and/or stenting (5 of 29), peripheral angioplasty (5 of 29), embolization (3 of 29), renal transplant arterial intervention (3 of 29), and venous thrombolysis (1 of 29).

The average pre-procedure serum creatinine value for all patients was 2.55 mg/dL. The pre-procedure value represents the value obtained on the day of the procedure in all cases. The average 24-hour post-procedure serum creatinine value was 2.28 mg/dL, which represents an average decrease of 12%. The patients were placed into four groups based on the severity of their renal dysfunction at the time of the procedure. The pre-procedure

serum creatinine values, the historical maximum serum creatinine values, and the average amount of contrast used for the patient's procedure in each group are summarized in Table 1. The number and percentage of patients in each group who had a decrease of greater than or equal to 0.2 mg/dL, an increase of greater than or equal to 0.2 mg/dL, or no change in the serum creatinine value at 24 hours is summarized in Table 2. The average values and range of values for any decrease or increase in serum creatinine is also summarized in Table 2. "No change" in serum creatinine was defined as a value at 24 hours that was less than or equal to 0.1 mg/dL different from the pre-procedure value. Twenty-eight of the 29 patients had a serum creatinine value obtained at 24 hours. One patient with a starting serum creatinine value of 2.7 mg/dL had an outpatient angiogram and did not return until twelve days later for a coronary angiogram at which time his creatinine value had dropped to 2.4 mg/dL. Of the 28 creatinine values recorded at 24 hours, 16 had decreased, 9 had not changed, and 3 had increased.

Three patients had an increase in serum creatinine values. One patient had a serum creatinine value increase of 0.3 mg/dL the day after contrast was administered, and was at the same level five days later. It was felt that this patient's serum creatinine increase was due to the contrast exposure. The other two patients had more marked increases in serum creatinine values. One was a patient with a transplant kidney who had a severe post-biopsy bleed with prolonged hematuria, an obstruction of the collecting system by clot, and an eventual percutaneous nephrostomy drainage catheter placement followed by arteriography and embolization of a pseudoaneurysm. The serum creatinine value increase at 24 hours was 0.2 mg/dL. The maximal increase was 1.5 mg/dL (2.7 to 4.2 mg/dL) that occurred on days four and five post-procedure. The serum creatinine value eventually stabilized at 3.3 mg/dL on day 32. The patient's course was complicated by rejection and eventual loss of the kidney.

The third patient who had an increase in serum creatinine value was scheduled to undergo bilateral renal artery stenting for azotemia. One kidney showed markedly better function and it was stented first. The procedure, however, was complicated by what appeared angiographically to be diffuse embolization or spasm of peripheral branches followed by stent thrombosis. The thrombosis was immediately opened with thrombolytics. The patient had a pre-procedure serum creatinine value of 3.5 mg/dL. Twenty-four hours after the procedure, the value had risen to 4.4 mg/dL and peaked at 5.8 mg/dL two days after the procedure. However, the patient did not require dialysis and the serum creatinine value eventually returned to a stable value of 3.7 mg/dL at twenty-one days, and then slowly decreased to 2.6 mg/dL after two months. Therefore, in the first week after contrast medium administration, there were only two patients (2 of 29 or 7%) whose serum creatinine value rose above 0.5 mg/dL, the threshold most commonly used to define renal failure in recent studies, but no patient whose renal failure could be definitively attributed to the contrast.

Two patients in group one had serum creatinine values just before the procedure of 1.3 and 1.4 mg/dL. They were included in this analysis and were chosen to receive fenoldopam because they were hypertensive diabetics whose most recent serum creatinine values before the day of the procedure had been 1.5 and 1.6 mg/dL respectively.

Two patients were of particular interest to us in that they had angiographic procedures both with and without fenoldopam during the period of the analysis. One patient had a history of severe neurofibromatosis with multiple pseudo- and true aneurysms of the intercostal arteries that bled spontaneously causing life-threatening hemothoraces. On one occasion, with a serum creatinine value of 5.8 mg/dL, the patient underwent a complex two-day attempt to embolize all of his intercostal arteries. He received a continuous fenoldopam infusion during the two days. Twenty-four hours after the second day of angiography, his serum creatinine value was 3.9 mg/dL and then 4.2 mg/dL at 48 and 72 hours. After he rebled on day three, he underwent repeat angiography and embolization without fenoldopam at the request of the referring service. One day later, without any other obvious clinical problems to negatively impact his renal function, his serum creatinine value had risen to 6.6 mg/dL, which was treated with three episodes of acute dialysis over one week. His course continued to deteriorate and he died two months later having never recovered his renal function. The second patient had an angiogram to evaluate possible atherosclerotic stenoses in his pelvic and renal arteries. He received fenoldopam and had a decrease in serum creatinine value from 2.7 mg/dL pre-procedure to 2.4 mg/dL twelve days later. He required a coronary angiogram at that time for which he did not receive fenoldopam. Twenty-four hours later, his serum creatinine value had risen to 2.6 mg/dL.

Six of the 29 patients were not able to reach the maximal fenoldopam dose of 0.5 g/kg/min. The average fenoldopam dose achieved was 0.46 g/kg/min, which indicates that most patients were able to achieve a dose close to or at the maximal dose of 0.5 g/kg/min. The average decrease in systolic pressure for all patients was 27.9 mm Hg. The average decrease in systolic pressure for those patients who reached the maximum dose of 0.5 g/kg/min was 22.9 mm Hg. The average drop in systolic blood pressure for patients who did not achieve the maximal dose of 0.5 g/kg/min was 44 mm Hg. Most patients were able to be treated with one or two vials of fenoldopam with a resulting cost in our hospital of \$200.00 to \$400.00.

Discussion

Contrast-associated Nephropathy and Acute Renal Failure

The reported incidence of contrast-associated nephropathy varies from 0% [8] to 93% [9]. This marked disparity reflects the differences between the various studies in the criteria used to define acute renal failure, the patient populations, the pre- and post-contrast treatment regimens, and the percentages of patients in the study receiving intravenous or intraarterial injections [10]. Approximately 10% of cases of acute renal failure are caused by the administration of contrast media, an overwhelming incidence that surpasses the incidence due to aminoglycoside antibiotics [11]. As the third most common cause of hospital-acquired acute renal failure [11], and the fourth most common cause of drug-induced acute renal failure [12], contrast-associated nephropathy is a significant problem for all physicians, especially radiologists and interventional cardiologists. A variety of risk factors have been shown to increase the incidence of contrast-associated nephropathy including pre-existing renal disease, diabetes mellitus, dehydration, multiple myeloma, large or recurrent doses of contrast medium, peripheral vascular disease, hypertension, proteinuria, concomitant administration of other nephrotoxic drugs, and age exceeding 60 years old [13]. However, the highest risk group is those patients with multiple risk

factors, especially a combination of diabetes and renal dysfunction [14]. In the highest risk groups, the incidence of contrast-associated nephropathy appears to be between 10% and 35% [1, 15], and in one study, in which ionic contrast media were used, as high as 80% [16]. The incidence of contrast-associated nephropathy in patients with no risk factors is less than 1% [17].

The exact mechanism of contrast-associated nephropathy remains poorly understood. It has been shown that contrast agents have various deleterious effects on the kidney. Today, the most widely accepted theory [18] is that the negative effect of contrast is primarily due to its hemodynamic consequences which consist of an initial brief rise in renal blood flow followed by a prolonged fall and gradual return to baseline [19]. The vasoconstrictive phase lasts for at least two hours, and one recent study (Tumlin JA et al., presented at the Society of Cardiovascular and Interventional Radiology meeting, March 1999) has indicated that it may extend out three to four hours after contrast administration. Most important, animal models indicate that the blood flow is particularly impaired to the outer portion of the medulla where the majority of the metabolic effort involving ion exchange occurs [20]. This reduction in medullary blood flow appears to drop the tubular cells, particularly those in the thick ascending limb, below some sort of ischemic threshold where cellular damage ensues. This damage is likely mediated by free radicals, which is one explanation for the profound effect noted in the recent study [1] using n-acetylcysteine, which is a free radical scavenger. Histologically, damage is often associated with a pattern of vacuolization in the affected tubular cells that has been described as “osmotic nephrosis.” The exact roles of osmolarity and chemotoxicity in this process and the contributions of osmolarity, chemotoxicity, and hemodynamic alterations to the ischemic changes that occur at the tubular level are still unresolved. It appears likely that the explanation for contrast-associated nephropathy will involve an interaction of factors such as reduced blood flow, medullary hypoxia, concentration of contrast, and the time contrast remains in contact with critical tissues.

The definition of what constitutes renal failure in patients with contrast-associated nephropathy has been the subject of extensive debate. Some authors advocate using absolute increases in serum creatinine, while others advocate using percentages of change from baseline. Definitions range from a severe change of an increase of at least 88 $\mu\text{mol/l}$ (1 mg/dL) or a 50% increase above baseline, to a less severe and more widely accepted limit of an increase of 44 $\mu\text{mol/l}$ (0.5 mg/dL) or a 25% above baseline [10]. In order to achieve a physiologically meaningful definition, a combination of absolute and percentage increases may be necessary. Interestingly, the most recent studies appear to have settled on a simple definition of renal failure as being an increase of serum creatinine at 48 hours of 0.5 mg/dL over baseline. Because a pure and objective definition of acute renal failure remains to be established, we elected to simply report the absolute values of the change in serum creatinine in our patients.

Previous Attempts to Prevent Contrast-associated Nephropathy

Before the recent study by Tepel et al [1] using n-acetylcysteine, many agents had been unsuccessfully investigated as potential therapeutic drugs for the prevention or treatment or both of contrast-associated nephropathy. Diuretics (mannitol, furosemide), vasoactive

agents (calcium channel blockers, atrial natriuretic peptide), and dopamine have shown promise in animal models [21-23]; however, none of these therapies has been consistently found to prevent or improve contrast-associated nephropathy in humans. Some agents, such as mannitol, are clearly detrimental in some high-risk groups. Nonspecific stimulation of dopamine receptors by so-called “renal doses” of dopamine is known to increase renal blood flow and glomerular filtration rate [24]. Unfortunately, this has not been a consistent and reproducible finding in all patient groups. This may be due to the contradictory effect of stimulation of dopamine type 1 (DA-1) receptors that increase renal blood flow, and dopamine type 2 (DA-2) receptors that decrease renal blood flow. In addition, some studies have used dopamine doses of 3 to 4 g/kg/min which would have resulted in alpha-receptor stimulation, and therefore, potential renal vasoconstriction [21, 24]. No studies of dopamine have demonstrated an unequivocally positive effect on contrast-associated nephropathy.

Fenoldopam and Contrast-associated Nephropathy

Even though it is closely related to dopamine, fenoldopam is a pure DA-1 receptor agonist that appears to have physiologic effects distinctly different from and more specific than dopamine. Therefore, fenoldopam may have a positive role in the treatment and prevention of contrast-associated nephropathy. Fenoldopam produces vasodilatation in vessels rich in DA-1 receptors, such as those in the kidney, mesenteric circulation, and periphery. Even at high doses, it does not stimulate DA-2 or adrenergic receptors [25, 26]. The Federal Drug Administration has approved fenoldopam for hypertension control because of its effect on peripheral DA-1 receptors. Fenoldopam potently relaxes both renal afferent and efferent arterioles in vitro [27]; however, in vivo it appears to preferentially vasodilate efferent arterioles [28]. This gives rise to an interesting finding that although renal blood flow increases markedly, glomerular filtration rate is frequently unaffected. Animal testing with fenoldopam has indicated it is six times more potent than dopamine in increasing renal blood flow and decreasing renal vascular resistance, and unlike other vasodilators that have been studied, it appears to induce a preferential increase in flow to the critical medullary regions [29]. Although there is, as of yet, no definite proof that this effect will result in the hoped for amelioration or prevention of contrast-associated nephropathy, anecdotal evidence such as our case series and early animal studies are quite promising. Data obtained from an experimental study by Bakris et al [30] using fenoldopam, indicate that selective DA-1 receptor stimulation prevents contrast-associated decreases in renal blood flow in volume depleted dogs. This effect was achieved at extremely low doses of 0.01 g/kg/min, which has a minimal effect on increasing renal blood flow and no effect on blood pressure.

In healthy volunteers, fenoldopam produces a dose-related increase in renal blood flow of up to 75% at a dose of 0.5 g/kg/min [31]. No increase in renal blood flow occurs above this level. Most of the effect, approximately 80%, is achieved at a dose of 0.3 g/kg/min [32], which implies that it may not be necessary to push all or most patients to the 0.5 g/kg/min level to obtain an adequate hemodynamic effect. Although glomerular filtration rate at doses of 0.3 to 0.5 g/kg/min is unchanged, urine volume and water and sodium excretion are all increased. This may have a protective effect by preventing sludging and obstruction of the tubules. Although fenoldopam was initially introduced in the 1960s as an antihypertensive agent, the doses which we have used to increase renal

blood flow (up to a maximum of 0.5 g/kg/min) are in the lower portion of the dose range used to treat hypertensive crises, which extends from 0.3 g/kg/min to a maximum of approximately 1.6 g/kg/min. Doses of 0.3 to 0.5 g/kg/min, which in hypertensive individuals cause significant reduction in blood pressure, are associated with no change in systolic blood pressure and with minimal reduction in diastolic blood pressure in normotensive individuals [32].

Studies of fenoldopam in hypertensive individuals have indicated that at doses of 0.3 to 0.5 g/kg/min, systolic blood pressure decreases by an average of 15-20 mm Hg and diastolic pressure by an average of 10-15 mm Hg. For this reason, any use of the drug to increase renal blood flow in hypertensive patients requires monitoring as the doses are increased to levels where an antihypertensive effect can be expected to occur. Although the levels of hypotension that are induced are not dangerous in most cases, a systolic blood pressure of less than 100-110 mm Hg could decrease renal perfusion pressure to a point where the protective effect of fenoldopam on the kidney may be lost. In addition, there is a slight tachycardia induced by the drop in blood pressure. This tachycardia may be norepinephrine related and could result in worsening heart failure in patients who have severe baseline heart failure. For this reason, fenoldopam needs to be used with caution and at potentially lower doses in patients with severe congestive heart failure.

The clinical activity of fenoldopam, which is administered intravenously, begins almost immediately and is clearly noticeable by five minutes. The antihypertensive effect becomes stable within 15-20 minutes after initiation of the drug, which means that blood pressure monitoring every 15-20 minutes is reasonable. At doses less than or equal to 0.1 g/kg/min, effects on blood pressure are minimal. If the drug is started at lower doses, such as 0.1 g/kg/min, and increased slowly into the 0.3 to 0.5 g/kg/min range, the blood pressure effects are less pronounced than if a higher dose is used as the starting dose. With this method, the effects are also easily controlled, even in those patients who have high blood pressure as a baseline. The drug has no rebound effect and can be stopped at any time. The elimination half-life is approximately 5-10 minutes, and therefore the antihypertensive effect will disappear rapidly once the drug is stopped. The drug is metabolized quickly and is not dependent upon the cytochrome P450 enzyme system in the liver. Therefore, no dosage adjustment is necessary for patients who have liver or kidney failure. To date, no interactions with other drugs have been demonstrated.

Our data represents only anecdotal evidence, because ours is a retrospective analysis of a completely uncontrolled, particularly high-risk group of patients undergoing a diverse set of procedures. No concurrent control group was chosen for comparison since all patients at highest risk during this time interval were treated. No historical controls were analyzed as the inherent biases of trying to select a historical control group make the scientific rigor of such an exercise dubious. However, some degree of historical comparison may be valid since many interventionalists have experience with this type of patient, particularly in modern times. There are published reports that 25-35% of high-risk patients for contrast-associated nephropathy reach a threshold at which they are defined as having acute renal failure. However, in addition, there is a much larger group with which we are all familiar, up to 75% in one series [33], who have a small early "bump" in serum creatinine values that may not actually lead to a diagnosis of acute renal failure.

This early rise in the first 24 to 48 hours was not seen in 25 of the 28 patients who had early post-procedure serum creatinine values, and as such, led to a significant change in attitude of the interventionalists doing these procedures. The normal anxiety about such cases was replaced with an almost eagerness to see if the results could be replicated. Interventional radiologists have many other means to help reduce the incidence of contrast-associated nephropathy. They can eliminate the “nothing by mouth after midnight” order in favor of an order that allows clear liquids up to two hours before the procedure and increase intravenous hydration. They can eliminate potentially nephrotoxic drugs for the 24 hours before contrast administration. They can use small doses of contrast with careful digitally subtracted filming technique. And finally, they have the option that we frequently utilized during this period, an option not available to cardiologists, neurointerventionalists and those supervising contrast enhanced CT studies, of using carbon dioxide and gadolinium as alternative contrast agents. As such, the need for chemical adjuncts to ameliorate the negative effects of contrast may be much less in interventional radiology than other areas where iodinated contrast is used.

An increase in serum creatinine that was definitively due to contrast was seen in only 4% (1 of 28) of the patients. In such high risk patients as ours, this rate is exceptionally low and the effect was not only seen at 24 hours. Sixteen patients had serum creatinine values obtained between three and seven days post-procedure when the maximal elevation of serum creatinine value should occur. Only one patient who had either no change or a decrease in serum creatinine at 24 hours had a later increase, and this occurred in a patient who had noted a 0.1 mg/dL rise at 24 hours. The maximal rise in this patient was 0.3 mg/dL. In addition, we have previously published our results in trans-jugular intrahepatic portosystemic shunt patients with combined hepatic and renal dysfunction demonstrating 100% mortality at 6 months [34]. Of the six patients with this same type of hepato-renal dysfunction who received their trans-jugular intrahepatic portosystemic shunt with fenoldopam assistance, one died of causes unrelated to liver or renal dysfunction, and three have outlived the six month limit which we regard as extremely important.

Conclusion

Our experience would suggest that fenoldopam may be of distinct benefit to high-risk patients who need intravascular contrast. It may be especially beneficial to those patients who receive a large contrast dose like complex patients undergoing peripheral or coronary interventions and/or computerized tomography. Although it is impossible on the basis of anecdotal case reports to determine whether or not fenoldopam was the primary reason for the marked protective effect seen in our patients, the results are promising enough to indicate that a careful prospective randomized trial of fenoldopam versus hydration is warranted.

References

- Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* **2000**;343:180-184
- Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* **1994**;331:1416-1420
- Gare M, Haviv YS, Ben-Yahuda A, et al. The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. *J Am Coll Cardiol* **1999**;34:1682-1688
- Elliot WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. *Circulation* **1990**;81:970-977
- Jorkasky DK, Audet P, Shusterman N, et al. Fenoldopam reverses cyclosporine-induced renal vasoconstriction in kidney transplant recipients. *Am J Kidney Dis* **1992**;19:567-572
- Schuster HP, Suter PM, Hemmer M, Clemens R, Bodmann KF, Romand J. Fenoldopam improves renal dysfunction secondary to ventilation with PEEP. *Intensive Care Med* **1991**;28:348-355
- Panacek EA, Bednarczyk EM, Dunbar LM, Foulke GE, Holcslaw TL. Randomized, prospective trial of fenoldopam vs sodium nitroprusside in the treatment of acute severe hypertension. Fenoldopam Study Group. *Acad Emerg Med* **1995**;2:959-965
- Cruz C, Hricak H, Samhouri F, Smith RF, Eyster WR, Levin NW. Contrast media for angiography: effect on renal function. *Radiology* **1986**;158:109-112
- Harkonen S, Kjellstrand CM. Exacerbation of diabetic renal failure following intravenous pyelography. *Am J Med* **1977**;63:939-946
- Jakobsen JA. Renal effects of iodixanol in healthy volunteers and patients with severe renal failure. *Acta Radiol Suppl* **1995**;399:191-195
- Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* **1983**;74:243-248
- Kleinknecht D, Landais P, Goldfarb B. [Acute renal failure associated with drugs or iodinated contrast media. Results of a cooperative multicentric study by the Nephrology Society]. [French] *Nephrologie* **1986**;7:41-46
- Berkseth RO, Kjellstrand CM. Radiologic contrast induced nephropathy. *Med Clin North Am* **1984**;68:351-370
- Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* **1989**;320:143-149
- Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int* **1995**;47:254-261
- Weinrauch LA, Healy RW, Leland OS Jr, et al. Coronary angiography and acute renal failure in diabetic azotemic nephropathy. *Ann Intern Med* **1977**;86:56-59
- Barrett BJ. Contrast nephrotoxicity. *J Am Soc Nephrol* **1994**;5:125-137
- Heyman SN, Reichman J, Brezis M. Pathophysiology of radiocontrast nephropathy: a role for medullary hypoxia. *Invest Radiol* **1999**;34:685-691
- Tornquist C, Almen T, Golman K, Holtas S. Renal function following nephroangiography with metrizamide and iohexol. Effects on renal blood flow, glomerular permeability and filtration rate and diuresis in dogs. *Acta Radiol Diagn* **1985**;26:483-489

- Nygren A. Contrast media and regional renal blood flow. A study of the effects of ionic and non-ionic monomeric and dimeric contrast media in the rat. *Acta Radiol Suppl* **1992**;378:123-135
- Conger JD, Falk SA, Yuan BH, Shrier RW. Atrial natriuretic peptide and dopamine in a rat model of ischemic acute renal failure. *Kidney Int* **1989**;35:1126-1132
- Thomsen HS, Dorph S, Mygind T, et al. Intravenous injection of ioxilan, iohexol and diatrizoate. Effects on urine profiles in the rat. *Acta Radiol* **1988**;29:131-136
- Nakamoto M, Shapiro JI, Shanley PF, Chan L, Schrier RW. In vitro and in vivo protective effect of atriopeptin III on ischemic acute renal failure. *J Clin Invest* **1987**;80:698-705
- Lass NA, Glock D, Goldberg LI. Cardiovascular and renal hemodynamic effects of intravenous infusions of the selective DA1 agonist, fenoldopam, used alone or in combination with dopamine and dobutamine. *Circulation* **1988**;78:1310-1315
- Singer I, Epstein M. Potential of dopamine A-1 agonists in the management of acute renal failure. *Am J Kidney Dis* **1998**;31:743-755
- Hahn RA, Wardell JR, Sarau HM, Ridley PT. Characterization of the peripheral and central effects of SK&F 82526, a novel dopamine receptor agonist. *J Pharmacol Exp Ther* **1982**;223:305-313
27. Lokhandwala MF, Amenta F. Anatomical distribution and function of dopamine receptors in the kidney. *FASEB J* **1991**;15:3023-30
28. Edwards RM. Comparison of the effects of fenoldopam, SK & F R-87516 and dopamine on renal arterioles in vitro. *Eur J Pharmacol* **1986**;126:167-170
29. Kien ND, Moore PG, Jaffe RS. Cardiovascular function during induced hypotension by fenoldopam or sodium nitroprusside in anesthetized dogs. *Anesth Analg* **1992**;74:72-78
30. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. *Kidney Int* **1999**;56:206-210
31. Allison NL, Dubb JW, Ziemniak JA, Alexander F, Stote RM. The effect of fenoldopam, a dopaminergic agonist, on renal hemodynamics. *Clin Pharmacol Ther* **1987**;41:282-288
32. Mathur VS, Swan SK, Lambrecht LJ, et al. The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. *Crit Care Med* **1999**;27:1832-1837
33. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med* **1989**;110:119-124
34. Nazarian GK, Ferral H, Castaneda-Zuniga WR, et al. Development of stenoses in transjugular intrahepatic portosystemic shunts. *Radiology* **1994**;192:231-234

Table 1. Categorization of patients based on severity of renal dysfunction at time of interventional radiologic procedure.

		Serum creatinine values before procedure	Maximum historical serum creatinine values Avg (range)	Average dose of contrast material (ml)
	<u>n</u>	Avg (range)		
Group 1	11	1.6 (1.3-1.9)	3.1 (1.5 - 5.7)	96
Group 2	10	2.4 (2.0-2.8)	4.7 (2.7 - 7.7)	104
Group 3	5	3.3 (3.1-3.5)	5.2 (3.4 - 5.8)	105
Group 4	3	5.0 (4.0-5.8)	8.1 (6.9 - 9.4)	113
Total	29	2.55 (1.3-5.8)	4.6 (1.5 - 9.4)	102

Table 2. Summary of pre- and 24 hours post-procedure creatinine values and changes

		Serum creatinine values before procedure Avg	Serum creatinine values 24 hours post-procedure Avg (range)	# (%) of pts with decreased creatinine values	Amount of decrease in serum creatinine values mg/dL Avg (range)	# (%) of pts with increased creatinine values	Amount of increase in serum creatinine values mg/dL
Group 1	11	1.6	1.5 (1.1 - 2.2)	6 of 11 (55%)	0.3 (0.2 - 0.6)	1 of 11 (9%)	0.3
Group 2	9	2.4	2.2 (1.6 - 3.1)	4 of 9 (44%)	0.4 (0.2 - 0.7)	1 of 9 (11%)	0.2
Group 3	5	3.3	3.1 (2.2 - 4.4)	3 of 5 (60%)	0.7 (0.4 - 1.0)	1 of 5 (20%)	0.9
Group 4	3	5	4.1 (3.5 - 5.0)	3 of 3 (100%)	0.9 (0.5 - 1.4)	0 of 3 (0%)	0
Total	28	2.5	2.3 (1.4 - 5.0)	16 of 28 (55%)	0.55 (0.2 - 1.4)	3 of 28 (10 %)	0.5 (0.2-0.9)