Kidney International, Vol. 41 (1992), pp. 1274–1279

CLINICAL INVESTIGATION

Contrast nephropathy in patients with impaired renal function: High versus low osmolar media

BRENDAN J. BARRETT, PATRICK S. PARFREY, HILARY M. VAVASOUR, JACKIE MCDONALD, GLORIA KENT, DONNA HEFFERTON, FRANK O'DEA, ERIC STONE, RAJ REDDY, and PATRICK J. MCMANAMON

Divisions of Nephrology and Cardiology, Departments of Medicine and Radiology, The General Hospital, The Health Sciences Centre, Memorial University, St. John's, Newfoundland, Canada

Contrast nephropathy in patients with impaired renal function: High versus low osmolar media. Prescription of low osmolar contrast to prevent nephrotoxicity in subjects with pre-existing renal impairment is costly and has not been clearly shown to be effective. We entered 249 subjects with a pre-contrast serum creatinine greater than 120 μmol/liter (1.35 mg/dl) having cardiac catheterization or intravenous contrast into a randomized controlled trial comparing high and low osmolar contrast. The outcome assessed was a rise in serum creatinine repeated 48 to 72 hours after contrast. A further 117 patients entered the non-randomized prospective arm of the study. In the randomized study the serum creatinine rose by at least 25% after contrast in 8 of 117 (6.8%) given high and in 5 of 132 (3.8%) given low osmolar contrast ($P > 0.05$, one-tailed 95% confidence interval for the difference 3 to 7.8%). More severe renal failure (greater than 50% increase in serum creatinine) after contrast was uncommon (3.4% with high and 1.5% with low osmolar contrast). A rise in serum creatinine after contrast was significantly associated with the severity of the pre-contrast renal impairment and the presence of diabetes mellitus, but not with type of contrast. Diabetics with a serum creatinine greater than 200 μmol/liter (2.25 mg/dl) pre-contrast had a highest risk of deterioration in renal function after contrast. We conclude that in patients with pre-existing renal impairment the incidence of contrast nephropathy was not significantly different comparing high osmolar and nonionic contrast. The potential benefit of nonionic contrast in moderate renal impairment is likely to be small, but trials in diabetics with severe renal impairment should be undertaken urgently.

Contrast nephropathy may be defined as an acute toxic nephropathy due to radiographic contrast media. There has been considerable confusion in the literature about the incidence of the condition [1]. We have previously shown that it is not common with normal pre-existing renal function, but that it is more frequent in patients with renal impairment, especially when due to diabetic nephropathy [2, 3].

There has been difficulty in establishing an animal model of contrast nephropathy [4]. This has hindered efforts to investigate its pathogenesis and has led some to question the existence of the condition [5]. Nevertheless, contrast has been shown to have toxic effects in rabbits whose kidneys have been subjected to other stresses [6].

It was expected that nonionic low-osmolar contrast would be less nephrotoxic than ionic high-osmolar media. Some [7–9], but not all studies [10, 11] of contrast-induced enzymuria and proteinuria have suggested that low-osmolar media may be less nephrotoxic. A randomized trial in humans, mostly with normal renal function, did not find that low-osmolar media were less nephrotoxic [12]. In a noncomparative study, low-osmolar contrast was associated with a 50% incidence of a 25% rise in serum creatinine after cardiac catheterization in patients with advanced diabetic nephropathy [13]. A randomized trial in patients with pre-existing renal impairment undergoing cardiac angiography found a statistically significantly smaller rise in serum creatinine at 24 hours after nonionic contrast than after ionic contrast [14]. The authors of the study concluded that nonionic contrast was less nephrotoxic than ionic, although there was not a significant reduction in the incidence of clinically important episodes of nephrotoxicity and no benefit was seen in insulin requiring diabetics [14]. A recent randomized trial of intravenous contrast in 101 patients with renal insufficiency suggested that high osmolar media were more likely than nonionic agents to cause mild exacerbation of renal insufficiency [15]. However, there were few cases of clinically important contrast nephropathy.

Because low-osmolar contrast is 10 to 20 times more expensive than high-osmolar contrast we compared several adverse reactions to these two agents in a randomized controlled trial of 3603 patients given intra-arterial or intravenous contrast, identified from a population of 5023 patients [16, 17]. Because patients with impaired renal function have an increased risk of contrast nephropathy [1–3], this cohort ($N = 573$) was identified and follow-up serum creatinine levels were ordered to determine the relative nephrotoxicity of the two classes of contrast media.

Methods

Research design and study population

This study was one component of a large randomized trial comparing ionic high-osmolar to nonionic low-osmolar contrast in a population of 5023 patients, using a variety of outcomes

Received for publication July 25, 1991
and in revised form October 5, 1991
Accepted for publication November 21, 1991

Table 1. Source of patients with pre-existing renal impairment who underwent cardiac angiography or had a procedure requiring intravenous contrast and entered the contrast nephropathy study

	Randomized			Non-randomized		
	Cardiac	i.v.	Total	Cardiac	i.v.	Total
Serum creatinine measured[a]	1490	2113	3603	366	1054	1420
Serum creatinine > 120 μmol/liter	153	222	375	57	105	162
Serum creatinine repeated after contrast	123 (80%)	126 (57%)	249 (66%)	50 (88%)	67 (64%)	117 (72%)

[a] All 5023 patients who entered the studies comparing high osmolar and nonionic contrast had serum creatinine measured. Only those with elevated serum creatinine entered the contrast nephropathy limb.

including systemic reactions, hemodynamic adverse events and severe symptoms [16, 17]. The trial was performed over the three years prior to February 1991 at a university based tertiary referral center. Patients having cardiac catheterization, intravenous pyelography, or CT scanning with contrast were eligible. All 5023 subjects entered in the study had their serum creatinine measured within 24 hours prior to contrast administration. Because the incidence of contrast nephropathy is very low in patients with normal renal function [1] only subjects whose serum creatinine exceeded 120 μmol/liter (1.35 mg/dl) had another measurement of serum creatinine ordered 48 to 72 hours after contrast. The population from which the study group was identified, and the proportion of the group who had follow-up serum levels measured is shown in Table 1.

The study population were stratified into those having cardiac angiography (N = 1856) and those having intravenous contrast (N = 3167) before randomization. No attempt was made to stratify for other factors related to nephrotoxicity because the pre-contrast serum creatinine levels were frequently not available until after the imaging procedure was completed.

Some subjects were excluded from the randomized trials [16, 17]. In the intravenous arm 1054 of 3167 patients were excluded because of prior severe reaction to contrast, active asthma, unavailability of low-osmolar contrast in a form suitable for the patient's investigation, and patient or physician refusal to enter the study. In the cardiac catheterization arm 366 of 1856 patients were excluded because of unstable angina, severe heart failure, or any of the above. No subject was excluded because of a perceived risk of nephrotoxicity. To allow recognition of bias we followed all subjects irrespective of randomization status. Table 1 shows the number of subjects who had a raised serum creatinine along with the number of subjects who had a second measurement of serum creatinine after contrast in the various groups.

Many subjects were outpatients and were not seen by a nephrologist prior to contrast. No routine prophylactic measures to prevent nephrotoxicity were employed before or after imaging. Before randomization, details of demographic, clinical (including any renal or cardiac disease and diabetes mellitus), and medication history were recorded by the research nurse. Subjects who had a 50% or greater rise in serum creatinine were seen by a nephrologist after imaging. The medical records of all subjects with at least a 25% increase in serum creatinine were reviewed by a nephrologist, blind to the contrast administered, to determine whether contrast was likely to have caused the increase.

Outcomes

Serum creatinine was measured by autoanalyzer in several different laboratories, as outpatient subjects attended their local hospitals for follow-up. We defined a case of contrast nephropathy as the unexplained occurrence of a 25% or greater increment in serum creatinine at 48 hours after contrast. We also report more severe degrees of deterioration in renal function. To facilitate comparison with other studies [12, 14], we report the number who had a rise of at least 44 μmol/liter (0.5 mg/dl) in serum creatinine, and the mean change in serum creatinine after each type of contrast.

Statistics and sample size

Incidence rates, means and standard deviations, medians and ranges are used as appropriate to describe the data. The frequency of events in the groups receiving high- and low-osmolar contrast was compared by chi-squared tests or Fisher's exact tests for 2 by 2 tables. Means were compared by t-tests for unpaired data, while medians were compared by Mann-Whitney U tests. We used a one-tailed α of 0.05 to declare significance and we report one-tailed 95% confidence intervals for differences between the randomized groups. We used multiple logistic (BMDP LR program, 1988) and multiple linear regression (SPSS-X, 1988) models to examine, and adjust for, the effect of covariates on the outcomes. Cross overs were handled by intention-to-treat analysis, but only one randomized subject received both types of contrast and had a subsequent rise in serum creatinine.

Before the study we estimated that the incidence of a 25% rise in serum creatinine after high-osmolar contrast would be 10% [2]. To detect a 50% reduction in this incidence with low-osmolar contrast, with a one-tailed α of 0.05 and a β of 0.2, we required to randomly assign 332 subjects to each type of contrast. However, enrollment in the contrast nephropathy study was stopped when the objectives of the two associated trials were achieved [16, 17]. Although the size of the sample that could be analyzed was less than anticipated, we felt that the data collected on these 366 subjects with renal impairment should be reported now, because the patient number studied is high in comparison to other studies, the incidence rates are lower than expected, the current literature is not definitive, and the subject is of clinical importance.

Table 2. Baseline comparison of the patients in the randomized trial[a]

	High-osmolar		Low-osmolar	
	$N = 117$	%	$N = 132$	%
Total				
Male	99	86.6	92	69.7
Diabetes mellitus	12	10.3	24	18.2
Serum creatinine > 200 μmol/liter	17	14.5	18	13.6
History of cardiac failure	18	15.4	20	15.2
Hypertensive	61	52.1	77	58.3
Bed bound in hospital	11	9.4	14	10.6
ACE inhibitor	13	11.1	15	11.4
Calcium channel blocker	49	41.9	48	36.4
Nonsteroidal anti-inflammatory	15	12.8	15	11.4
Diuretic	30	25.6	31	23.5
Type of investigation				
Cardiac catheterization	64	54.7	59	44.7
Intravenous pyelogram	19	16.2	34	25.8
Computed tomography	34	29.1	39	29.5
	Mean ± SD		Mean ± SD	
Age *years*	64.3 ± 10.7		64.0 ± 12.3	
Systolic blood pressure *mm Hg*	140.6 ± 26.5		142.8 ± 23.6	
Diastolic blood pressure *mm Hg*	75.9 ± 12.1		78.2 ± 13.0	
Weight *kg*	77.9 ± 12.6		75.1 ± 12.5	
	High-osmolar		Low-osmolar	
	Median	Range	Median	Range
Serum creatinine *μmol/liter*	138	120–685	138	120–572
Blood urea *mmol/liter*	9.8	4–47	9.9	4.7–44
Contrast volume *ml*	120	50–400	100	40–400

[a] All these patients had pre-contrast serum creatinine > 120 μmol/liter (1.35 mg/dl) and had follow-up serum creatinine performed 48 to 72 hours after contrast.

Table 3. Baseline characteristics of the patients who did not enter the randomized trial but whose renal function was prospectively followed after contrast

	High-osmolar		Low-osmolar	
	$N = 43$	%	$N = 74$	%
Total				
Male	36	83.7	47	63.5
Diabetes mellitus	4	9.3	11	14.9
Serum creatinine > 200 μmol/liter	13	30.2	15	20.2
History of cardiac failure	8	18.6	25	33.8
Hypertensive	20	46.5	51	68.9
Bed bound in hospital	5	11.6	22	29.7
ACE inhibitor	3	7.0	12	16.2
Calcium channel blocker	5	11.6	32	43.2
Nonsteroidal anti-inflammatory	9	20.9	10	13.5
Diuretic	13	30.2	29	39.2
Type of investigation				
Cardiac catheterization	1	2.3	49	66.2
Intravenous pyelogram	2	4.6	9	12.2
Computed tomography	40	93.1	16	21.6
	Mean ± SD		Mean ± SD	
Age *years*	66.4 ± 11.4		67.0 ± 11.8	
Systolic blood pressure *mm Hg*	136.0 ± 20.1		142.0 ± 29.5	
Diastolic blood pressure *mm Hg*	79.0 ± 11.7		75.0 ± 15.3	
	High-osmolar		Low-osmolar	
	Median	Range	Median	Range
Serum creatinine *μmol/liter*	159	120–502	141	120–65
Blood urea *mmol/liter*	11.8	6–32	10.3	5–66
Contrast volume *ml*	300	50–400	122.5	45–40

Results

Baseline comparison

Table 2 shows the baseline characteristics of the randomized subjects who had a measurement of serum creatinine after contrast. By chance more diabetics were given low-osmolar contrast, while cardiac angiography was the investigation performed in a greater proportion of those given high-osmolar contrast.

Table 3 shows the same profile of baseline characteristics for the subjects who were not entered in the randomized trial, but who did have a second determination of serum creatinine. In the early part of our study infusable low-osmolar contrast was not available for CT of the body [16]. These patients were more likely to have diseases associated with renal impairment. The profile of the subjects who had low-osmolar contrast reflects the fact that a majority had severe cardiac disease and had cardiac angiography. Therefore it is not surprising that both groups had higher serum creatinine levels than the corresponding randomized groups.

We examined the characteristics of those subjects who failed to have a second serum creatinine determination. In the randomized study these subjects differed from those having follow up in that a greater proportion had intravenous contras (76.2%), and were outpatients, while a lesser proportion (7.1% had a serum creatinine greater than 200 μmol/liter (2.25 mg/dl)

Outcome of the trial

The difference between the two randomized groups, in term of any of the outcome events, failed to reach statistical signi icance (Table 4). Although the incidence of minor changes i renal function after contrast was greater in the subjects wh were not randomized, more severe acute renal failure was nc significantly more common in these subjects (Table 4).

Following review of the records, it was felt that contrast wa unlikely to have been responsible for the 25% rise in serur creatinine after contrast in one subject randomized to higl osmolar contrast, in two subjects nonrandomly receiving higl osmolar contrast, and in one subject nonrandomly given low osmolar contrast. When these cases were excluded, th incidence of a 25% increment in creatinine was 6% (95% CI 2. to 11.9) in those randomized to high-osmolar, and 3.8% (95% C 1.2 to 8.6) in those randomized to low-osmolar contrast. Th corresponding figures for the non-randomized groups wer 18.6% (95% CI 8.4 to 33.4) with high-osmolar and 9.5% (95% C 3.9 to 18.5) with low-osmolar contrast.

The mean change in serum creatinine by 48 to 72 hours afte contrast was 3.5 μmol/liter (0.04 mg/dl) in those randomized t

Table 4. The incidence of outcome events in the trial before removal of cases where contrast was not felt to be the cause of the acute renal failure

	High-osmolar		Low-osmolar		95% CI for the reduction with low-osmolar
	$N = 117$	%	$N = 132$	%	%
Randomized subjects					
S_{Cr} rise of 25%	8	6.8	5	3.8	3.0 to 7.8
S_{Cr} rise of 50%	4	3.4	2	1.5	1.9 to 5.2
S_{Cr} rise of 44 μmol/liter	7	6.0	7	5.3	0.7 to 5.6
Dialysis required	1	0.8	0	—	0.8 to 2.1
	High-osmolar		Low-osmolar		
	$N = 43$	%	$N = 74$	%	
Non-randomized subjects					
S_{Cr} rise of 25%	10	23.3	8	10.8	
S_{Cr} rise of 50%	2	4.7	3	4.1	
S_{Cr} rise of 44 μmol/liter	7	16.3	8	10.8	
Dialysis required	0	—	2	2.7	

S_{Cr} is serum creatinine. Note that the 95% confidence intervals for the differences between the randomized groups are one-tailed.

Table 5. The incidence of a 25% rise in serum creatinine with high- or low-osmolar contrast in the randomized trial after stratification by serum creatinine and the presence of diabetes mellitus

Stratum	High-osmolar		Low-osmolar	
	N	%	N	%
Nondiabetic with serum creatinine < 200 > 120 μmol/liter	3/92	3.3	1/97	1.0
Diabetic with serum creatinine < 200 > 120 μmol/liter	0/8	—	2/17	11.8
Nondiabetic with serum creatinine > 200 μmol/liter	1/13	7.6	1/11	9.1
Diabetic with serum creatinine > 200 μmol/liter	3/4	75.0	1/7	14.3

high-osmolar and −1.5 μmol/liter (−0.02 mg/dl) in those randomized to low-osmolar contrast (95% confidence interval [CI] for the difference −6.1 to 16.1 μmol/liter = −0.07 to 0.18 mg/dl). The corresponding figures for the non-randomized groups were 17 μmol/liter (0.19 mg/dl) in the high-osmolar and 4 μmol/liter (0.04 mg/dl) in the low-osmolar group. Because serum creatinine is not linearly related to glomerular filtration rate, we also compared the response to the two types of contrast after inverse and logarithmic transformation of the data. This analysis also failed to reveal any statistically significant difference between the high- and low-osmolar media.

Multivariate analysis of the effect of contrast

Given the lack of statistically significant benefit with low-osmolar contrast, and the difference in the randomized groups at baseline which might have contributed to this situation, we analyzed the randomized subjects by multiple linear regression analysis. The change in serum creatinine after contrast served as the dependent. The independent variables used were the type and route of administration of contrast, presence of diabetes, and the pre-contrast serum creatinine. The type of contrast did not significantly predict the change in serum creatinine in these models.

Risk factors for contrast nephropathy

To identify factors which might predispose to contrast nephropathy and to examine the effect of low-osmolar contrast in various risks groups we stratified the randomized subjects into four groups: those with a pre-contrast serum creatinine between 120 and 200 μmol/liter (1.35 and 2.25 mg/dl) with and without diabetes, and those with a pre-contrast serum creatinine greater than 200 μmol/liter (2.25 mg/dl) with and without diabetes. The incidence of contrast nephropathy, as defined by a 25% increment in serum creatinine after high- or low-osmolar contrast, in each of the strata is shown in Table 5. These results suggest that those with more severe renal impairment, especially when due to diabetic nephropathy, are at the highest risk of contrast nephropathy. There is not a consistent trend to a lower incidence of contrast nephropathy with low-osmolar contrast across the strata but the lower incidence with low-osmolar contrast in the group with advanced diabetic nephropathy is interesting given the results of another recent trial [14].

When the data for all subjects, irrespective of randomization or type of contrast prescribed, was stratified and analyzed in the same fashion as for the randomized patients the results suggested even more strongly that the degree of renal impairment, especially in diabetics, is predictive of the risk for contrast nephropathy. The serum creatinine rose by more than 25% after contrast in 16 of 266 (6%) with a serum creatinine less than 200 μmol/liter (2.25 mg/dl) without diabetes, in 4 of 36 (11%) diabetics with a serum creatinine less than 200 μmol/liter (2.25 mg/dl), in 8 of 48 (16.7%) of those with a serum creatinine greater than 200 μmol/liter (2.25 mg/dl) without diabetes, and in 5 of 15 (33.3%) diabetics with a serum creatinine greater than 200 μmol/liter (2.25 mg/dl).

In a series of multiple linear and logistic regression models the only variables which were statistically significantly associated with a rise in serum creatinine after contrast were the severity of the pre-existing renal impairment and the presence of diabetes. In these models the type, volume, and route of administration of contrast did not add to the prediction of contrast nephropathy.

Discussion

Our randomized study failed to confirm a clinically important role for low-osmolar contrast in prevention of contrast nephropathy in subjects with renal impairment. This is compatible with the results of an earlier study which largely examined subjects with normal renal function [12]. Table 6 summarizes the results from the randomized trials of Taliercio et al [14], Harris et al [15] and the current trial, pooling data from 657 patients. The entry criteria was similar in the three studies: pre-contrast serum creatinine levels of >120 to 134 μmol/liter (1.35 to 1.5 mg/dl). However, less than 20% of the patients had severe renal impairment (pre-serum creatinine greater than 200 μmol/liter = 2.25 mg/dl). The incidence of clinically important acute renal failure (defined as >50% increase in serum creatinine after contrast) was not significantly different: 3.4% after high osmolar

Table 6. Clinically important contrast nephropathy in renal impairment: High osmolar vs. nonionic contrast

	High osmolar				Nonionic			
	>50% Rise in S_{Cr}[a]		Dialysis required		>50% Rise in S_{Cr}		Dialysis required	
Reference	*N*	%	*N*	%	*N*	%	*N*	%
Taliercio et al [14]	6/152	3.9	2/152	1.3	3/155	1.9	1/155	1
Harris et al [15]	1/50	2.0	0	0	1/51	2.0	0	0
Barrett et al	4/117	3.4	1/117	0.9	2/132	1.5	0	0
Total	11/319	3.4	3/319	0.9	5/338	1.5	1/338	0.3

[a] >50% increase in serum creatinine within two days of contrast administration

versus 1.5% after nonionic contrast. The relative risk of developing clinically important acute renal failure after high osmolar contrast compared to nonionic contrast was 2.27 (95% CI: 0.82 to 6.65). Therefore, we conclude that the potential benefit of nonionic contrast in preventing contrast nephropathy in patients with moderate pre-existing renal impairment is likely to be small.

However, given that the level of renal impairment, especially in diabetics, is the best predictor of contrast nephropathy and given the small number of patients studied with severe pre-existing renal failure further trials are indicated in patients, especially diabetics, with serum creatinine greater than 200 μmol/liter (2.25 mg/dl).

A limitation of our study is that it does not have sufficient power to exclude a 50% reduction in the incidence of contrast nephropathy, as assessed by any outcome, with low-osmolar contrast. Given the results, we would have required a sample size of over 1300 subjects per group to exclude such a benefit, using a rise of 25% in serum creatinine to diagnose a case of contrast nephropathy [18]. However, it is not likely that even such an expanded cohort of patients would alter our conclusions given the very low incidence of clinically important renal failure observed when the results of three recent studies are pooled (Table 6). Our study did have a power of greater than 0.8 to detect a true difference of at least 10 μmol/liter (0.11 mg/dl) in the change in serum creatinine after contrast between high- and low-osmolar media, and no such difference was found. This is contrary to the findings of another recent trial [14].

Although the data suggest that low-osmolar media may have some benefit, we cannot conclude that low-osmolar contrast prevents contrast nephropathy in subjects with impaired renal function. If the point estimates of incidence in our randomized trial (similar to the incidence observed when three recent studies are pooled) are correct, one would need to treat 53 subjects of the type in our randomized trial with low-osmolar contrast at a marginal cost of Canadian $4770 to prevent one case having a 50% rise in serum creatinine after contrast. If low-osmolar contrast was reserved for those with a pre-contrast serum creatinine of greater than 200 μmol/liter (2.25 mg/dl) with or without diabetes one would only need to treat 8 such subjects at a marginal cost of Canadian $720 to prevent one such event.

It is of interest that the incidence of contrast nephropathy was low in our subjects who did not receive any prophylactic treatment. In fact, our results are similar to those of others who employed a prophylactic fluid loading regimen [12]. While avoidance of dehydration is desirable the benefits of intentional fluid loading or any other prophylactic measure need to be established by adequate randomized controlled trials before routine use can be recommended.

We chose to use serum creatinine to measure outcome, even though it is an insensitive measure of renal function, as it has the advantages of being easy to measure and of being able to detect clinically important changes in renal function. Others have used enzymuria to compare the nephrotoxicity of high- and low-osmolar contrast, but the results have not been consistent and were often of dubious clinical relevance [7–11].

We conclude that the incidence of clinically important contrast nephropathy is low after both high and low-osmolar contrast media in subjects with moderate pre-existing renal impairment. Larger studies will be required to define the precise role of low-osmolar media for prevention of contrast nephropathy in subjects with more severe impairment of renal function. Since those with diabetic nephropathy seem to be at greatest risk [13], it would make most sense to conduct any further trials in such patients.

Acknowledgments

This research was funded by grants from Health and Welfare, Canada, The General Hospital, and The General Hospital Health Foundation. Dr. Barrett was a Kidney Foundation of Canada Fellow, and Mr. O'Dea a summer student funded by the Federal Challenge '90 program. The cardiologists who participated in this trial were Drs. E. Stone, C. McCallum, B. Sussex, M. Furey, A. Williams, B. Rose, and S. Missan. The radiologists who participated in this study were Drs. R. Reddy, P. McManamon, M. Mangan, T. Cummings, S. McMaster, and P. Collingwood.

Reprint requests to Dr. P.S. Parfrey, Division of Nephrology, The Health Sciences Centre, St. John's, Newfoundland, Canada, AIB 3V6.

References

1. Barrett BJ, Parfrey PS: Clinical aspects of acute renal failure following use of radiocontrast agents, in *Acute Renal Failure: Diagnosis, Treatment, and Prevention,* edited by Solez K, Racusen LC, New York, Marcel Dekker Inc, 1991, pp. 481–500
2. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon P: Radiocontrast induced renal failure in diabetes mellitus and in patients with pre-existing renal failure: A prospective controlled study. *N Engl J Med* 320:143–149, 1989
3. Cramer BC, Parfrey PS, Hutchinson TA, Baran D, Melanson DM, Ethier RE, Seely JF: Renal function following infusion

of radiologic contrast material: A prospective controlled study. *Arch Intern Med* 145:87–89, 1985
4. VAAMONDE CA, BIER RT, PAPENDICK R, ALPERT H, GOUVEA W, OWENS B, PARDO V: Acute and chronic renal effects of radiocontrast in diabetic rats: Role of anesthesia and risk factors. *Invest Radiol* 24:206–218, 1989
5. KATZBERG RW: What do we really know about contrast medium-induced acute renal failure? *Invest Radiol* 24:219–220, 1989
6. VARI RC, NATARAJAN LA, WHITESCARVER SA, JACKSON BA, OTT CE: Induction, prevention and mechanisms of contrast media-induced acute renal failure. *Kidney Int* 33:699–707, 1988
7. TORNQUIST C, HOLTAS S: Renal angiography with iohexol and metrizoate. *Radiology* 150:331–334, 1984
8. CAVALIERE G, ARRIGO G, D'AMICO G, BERNASCONI P, SCHIAVINA G, DELLAFIORE L, VERNAGHI D: Tubular nephrotoxicity after intravenous urography with ionic high-osmolal and nonionic low-osmolal contrast media in patients with chronic renal insufficiency. *Nephron* 46:128–133, 1987
9. SKOVGAARD N, HOLM J, HEMMINGSEN L, SKAARUP P: Urinary protein excretion following intravenously administered ionic and non-ionic contrast media in man. *Acta Radiol* 30:517–519, 1989
10. GALE ME, ROBBINS AH, HAMBURGER RJ, WIDRICH WC: Renal toxicity of contrast agents: Iopamidol, iothalamate, and diatrizoate. *Am J Radiol* 142:333–335, 1984
11. DONADIO C, TRAMONTI G, GIORDANI R, LUCCHETTI A, CALDERAZZI A, SBRAGIA P, BIANCHI C: Effects of contrast media on renal hemodynamics and tubular function: Comparison between diatrizoate and iopamidol. *Adv Exp Med Biol* 252:257–264, 1989
12. SCHWAB SJ, HLATKY MA, PIEPER KS, DAVIDSON CJ, MORRIS KG, SKELTON TN, BASHORE TN: Contrast nephrotoxicity: A randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med* 320:149–153, 1989
13. MANSKE CL, SPRAFKA JM, STRONY JT, WANG Y: Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 89:615–620, 1990
14. TALIERCIO CP, VLIETSTRA RE, ILSTRUP DM, BURNETT JC, MENKE KK, STRENSRUD SL, HOLMES DR: A randomized comparison of the nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography. *JACC* 17:384–390, 1991
15. HARRIS KG, SMITH TP, CRAGG HA, LEMKE JH: Nephrotoxicity from contrast material in renal insufficiency. *Radiology* 179:849–852, 1991
16. BARRETT BJ, PARFREY PS, VASASOUR HM, O'DEA F, KENT G, STONE E: A comparison of nonionic low-osmolar with ionic high-osmolar radiocontrast agents during cardiac catheterization. *N Engl J Med* 326:431–436, 1992
17. BARRETT BJ, PARFREY PS, MCDONALD J, HEFFERTON D, REDDY R, MCMANAMON P: A randomized trial of nonionic low-osmolar versus ionic high-osmolar radiocontrast for intravenous use in patients perceived to be at high risk. *Radiology* (in press)
18. DETSKY AS, SACKETT DL: When was a 'negative' clinical trial big enough? *Arch Intern Med* 145:709–712, 1985