Renal

RENAL FAILURE FOLLOWING RADIOLOGIC PROCEDURES

Cholesterol Emboli Syndrome

Medical Grand Rounds

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Radiologic procedures are currently a major cause of acute renal failure, but it is only in the relatively recent past that the magnitude of this problem has been appreciated. This grand rounds will review the current status of this disorder and describe in detail two varieties, namely, 1) radiocontrast-induced acute renal failure and 2) cholesterol emboli-induced acute renal failure following angiography.

Radiocontrast-induced acute renal failure

The recognition that radiocontrast is an important cause of acute renal failure is a relatively recent phenomenon. Isolated case reports of death, anaphylaxis, and renal failure following its use are rare, but it is only during the past 15-20 years that radiocontrast has achieved prominence as a major clinical cause of nephrotoxic acute renal failure. Of 129 consecutive cases of hospital-acquired renal insufficiency, radiocontrast studies were the cause in 16 patients (12%), ahead of the 9 cases (7%) of aminoglycoside nephrotoxicity (1) (Table 1). In the late 1960ties, reports appeared that patients with chronic renal failure and patients with diabetes mellitus were particularly at risk for the development of acute renal failure after exposure to radiocontrast. Initially, acute renal failure was thought to be a rare complication, but reports came in rapid succession confirming the widespread nature of the problem. Clinicians and radiologists alike have reevaluated the use of radiocontrast agents in the diagnosis of renal disease and in the diagnosis of non-renal disease in patients with impaired renal function. In the presence of renal insufficiency there is now a decided trend to avoid radiocontrast studies when alternative imaging procedures are available (e.g. ultrasonography and/or cystoscopy and retrograde pyelography to diagnose obstructive uropathy). Additional developments and applications of magnetic resonance imaging (MRI) may also lead to a lessening of the demand for radiocontrast agents in high risk patients. However, the overall usage of radiocontrast is probably increasing due to the requirement for angiography in connection with surgery and angioplasty on diseased vessels of the heart, kidneys and aorta.

TABLE I **Outcome of 129 Episodes of Acute Renal Insufficiency**

Cause of Renal Insufficiency	Episodes of Renal Insufficiency (no.)	No. of Patients Who Died
Decreased renal perfusion	54	19* (35%)
Major surgery	23	3 (13%)
Contrast media administration	16	1* (6%)
Aminoglycoside administration	9	1* (11%)
Hepatorenal syndrome	5	4 (80%)
Obstruction	3	0 (0%)
Vasculitis	2	0 (0%)
Renal embolus	1	0 (0%)
Cis-platinum administration	1	0 (0%)
Multifactoral	4	0 (0%)
Unknown	11	4 (36%)
Total	129	32 (24.8%)

* Includes one death from renal failure per se.

Incidence

The true incidence of radiocontrast-induced acute renal failure in the entire population at risk cannot be established with certainty from published literature, since incidence figures vary depending on the population studied and the definition of acute renal failure that is used (Table 2). The recent surge in reports of acute renal failure following radiocontrast agents might suggest that the incidence of this problem is increasing, especially in view of early reports that urographic studies in patients with chronic renal insufficiency were both efficacious and safe (2,3). However, a careful reading of these reports suggests that the same risk of renal damage was present then. In recent years, nephrotoxicity or acute renal failure has been defined variously as a rise in serum creatinine of 0.3 mg/dl (4,5), 0.5 mg/dl (6,7), 0.6 mg/dl (8), 1.0 mg/dl (9-14), 2.0 mg/dl (15-17), or a 50% increase in the baseline serum creatinine (18,19) during 1-5 days following exposure to radiocontrast agents. Byrd and Sherman (15) reported an overall incidence of acute renal failure of approximately 0.15% for urographic and tomographic studies and 0.53% for angiographic studies. Two aspects of this report suggest that these incidence figures may have been low estimates: 1) the study was a retrospective analysis only of cases severe enough to

Table 2
Radiocontrast-induced acute renal failure
Incidence

Rise in SCr	Interval (Days)	Procedure	Incidence (%)	Ref.
0.3 mg/dl	5	angiography	17	5
0.5 mg/dl	1	angiography	1	24
	2	cardiac cath		
		low risk	8-10	6
		high risk	15-17	
1.0 mg/dl	1-5	angiography		10
		(SCr≥ 2 mg/dl)	23	
	3	iv + arterial contrast		7
		high-risk	3	
	1	angiography		21,22
		saline expanded	0	
	2	angiography		20
		seriously ill	12	
	2	angiography		9
		non-azotemic	0.68	
		azotemic	17.4	
2.0 mg/dl	2	urography	0.15	15
		angiography	0.53	
Increase 50% >baseline	2	iv + arterial		19
		high-risk	8.8	
	2	CT scans	1	18

prompt nephrologic consultation by the primary physician, and 2) a rise of 2 mg/dl in serum creatinine was required during the 48 hours following the procedure to make a diagnosis of acute renal failure. These two factors in the study design would not detect mild cases of renal insufficiency. When the criteria for nephrotoxicity are more liberal, the incidence figures are higher. D'Elia et al (9) found that 0.68% of non-azotemic patients and 17.4% of azotemic patients had a 1 mg/dl rise in serum creatinine following non-renal angiography. Swartz et al (20) reported a 12% incidence of acute renal failure in seriously ill hospitalized patients using as their criterion a rise in serum creatinine of at least 1 mg/dl within 48 hours of the study. However, believing this to be an overestimate of the true incidence of acute renal failure following radiocontrast studies, Eisenberg et al (21) prospectively studied 100 consecutive patients undergoing major angiography using criteria similar to but not identical to that of Swartz and found no episodes of acute renal failure. This study was later extended to include data from 537 consecutive patients, and again demonstrated no episodes of acute renal failure (22). This latter study differed from that of Swartz et al (20) in that all patients were volume expanded with saline during angiography and the criterion for nephrotoxicity was more strict, (i.e. a rise in serum creatinine of 1 mg/dl within 24 hours of the study), a point for which the study was criticized (23). In another study done in response to the report by Swartz et al (20), Kumar et al (24) reported a serum creatinine rise of 0.5 mg/dl in only one patient during the 48 hours following 100 consecutive angiographic studies. Using even less stringent criteria for nephrotoxicity, Cochran et al (5) reviewed the records of 800 patients undergoing renal angiography to obtain 266 cases with pre- and post-angiography serum creatinine values. Using as the criteria for nephrotoxicity a rise in serum creatinine of 0.3 mg/dl or a greater than 20% rise of serum creatinine within 5 days of the procedure, they found an incidence of 17% (45/266). While sensitivity in case detection was improved by these less rigid criteria, the group probably included a number of patients with transient, volume depletion-induced elevations in serum creatinine.

Thus, the incidence figures for acute renal failure following radiocontrast administration are dependent on whether the patient has normal or abnormal renal function prior to the procedure and also on what arbitrary change in renal function (usually serum creatinine) is used to make the diagnosis.

Risk factors for radiocontrast-induced acute renal failure

The list of risk factors purported to predispose to radiocontrast-induced acute renal failure is long (Table 3) and includes age (5,14,15,17,20,25,26,27,28), renal insufficiency (5,9,14,15,17,20,25-32), diabetes mellitus

Table 3

Radiocontrast-induced acute renal failure
Risk factors

Age	Hyperuricemia
Renal insufficiency	Exposure to other nephrotoxins
Diabetes Mellitus	Repeated exposure to radiocontrast
Multiple Myeloma	Volume of contrast
Anemia	Intraarterial vs intravenous
Proteinuria	Male sex
Abnormal Liver Function	Cardiovascular disease
Volume Depletion	Hypertension
Dehydration	Renal transplantation

(10,11,14,15,17,20,25,26,28,30,32-37), multiple myeloma (38-41), anemia (32), proteinuria (5,17,42,20), abnormal liver function (20,42), volume depletion (27,32,43), dehydration (25,26,36,44,45), hyperuricemia (11,15,46), concomitant exposure to other nephrotoxins (33,34,36,44,46), repeated exposure to radiocontrast over a few days (4,5,15,42,45,46), volume of contrast (10,14,27,32,33,34,43,47), injection site, i.e. intraarterial vs intravenous (15,32), male sex (5), presence of cardiovascular disease (4,5,10,14,17,28,32,33,36,45), hypertension (4,5,17,45,46,48), and renal transplantation (49,50). Many of these risk factors may be covariate rather than independent. This probably accounts for reports that fail to confirm many of these as risk factors (9-11,51). Harkonen and Kjellstrand (11) were unable to make an association between radiocontrast acute renal failure and volume depletion, the dose of contrast, the use of concomitant nephrotoxic drugs, or hyperuricemia. Volume depletion and dehydration, often the result of purging enemas and restricted food and fluid intake prior to urographic and arteriographic studies, is probably only a contributing factor to radiocontrast induced acute renal failure. D'Elia et al (9) studied 378 hospitalized patients undergoing non-renal angiography and identified the presence of preexisting azotemia as the only risk factor predisposing to nephrotoxicity (defined as a rise in serum creatinine of 1 mg/dl or greater following the procedure). The volume of radiocontrast material injected, the site of injection, a history of prior cardiovascular disease, or diabetes mellitus were not significant factors in the development of acute renal failure. Miller et al (51) prospectively studied 200 patients requiring intravenous or intraarterial contrast and found no consistent change in renal function with increasing doses of contrast material (Figure 1). Also, in ten patients who underwent two procedures with only one day between them (Figure 2), there

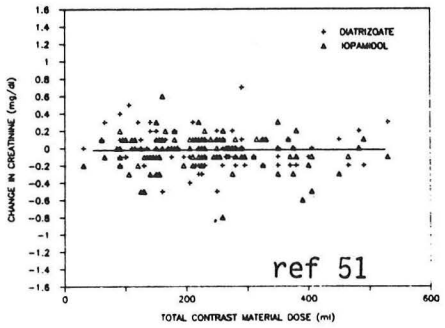


Figure 1

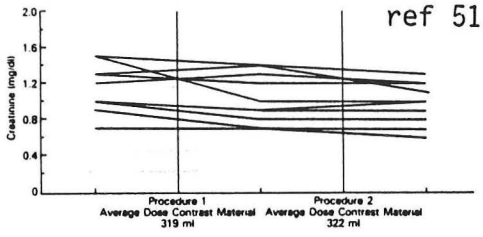
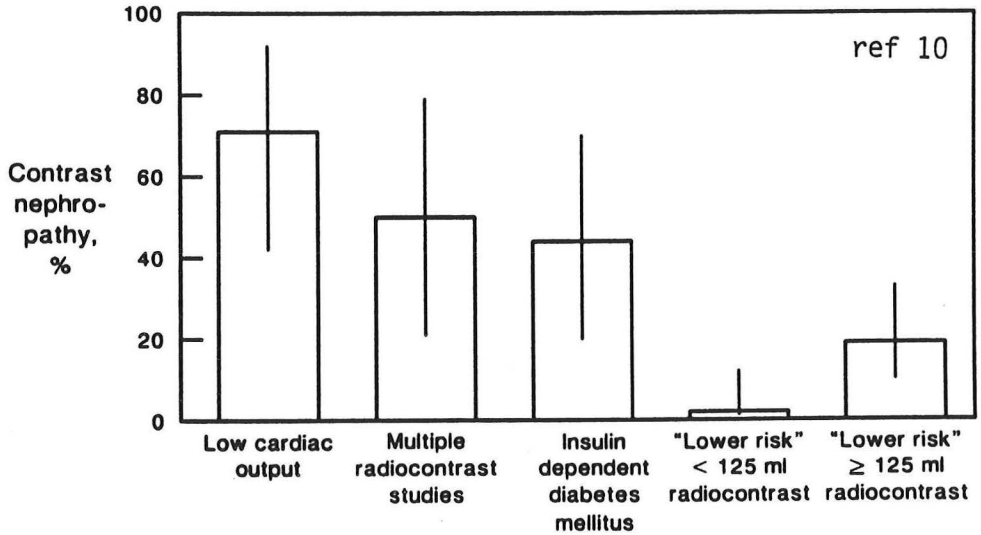


Figure 2

was no tendency toward deterioration of renal function. Cochran et al (5) studied the interdependency of risk factors in 45 patients who developed a significant elevation of serum creatinine (greater than 0.3 mg/dl) after an angiographic procedure. They found that age, proteinuria, abnormal baseline serum creatinine, use of Renografin 76, and preexisting renal disease were the five independent risk factors. These five clinical factors were those most likely to predict patients who would have an increase in serum creatinine after angiography. Taliercio et al (10) have shown that class IV heart failure is an independent risk factors for contrast-induced acute renal failure, particularly when the amount of contrast exceeds 125 ml (Figure 3). They reported a 23% incidence of contrast nephropathy (>1 mg/dl rise in serum creatinine) in 139 patients with pre-existing abnormal renal function, (serum

Figure 3 Percentage of patients developing contrast nephropathy in select clinical subsets. Patients at lower risk are without low cardiac output, multiple studies, or insulin-dependent diabetes mellitus. Bars show 95% confidence intervals.



creatinine ≥2mg/dl) who underwent cardiac angiography. The mean increment in serum creatinine was 2.6 mg/dl, the time to peak serum creatinine was 2.8 days, and 9% developed anuria or oliguria. Similarly, Gomes et al (14) showed an increased incidence of contrast induced acute renal failure in patients receiving digoxin for congestive heart failure or arrhythmias.

Radiocontrast acute renal failure and diabetes

Another factor that has been singled out in most large reviews as a major risk factor is the presence of diabetes. As recently as 15 years ago, it would have been considered standard procedure, and in some cases mandatory, that a diabetic patient with progressively worsening renal function have an excretory urogram to rule out a reversible form of renal failure (e.g., obstructive uropathy). Unfortunately, this practice may have produced more renal failure than it alleviated. It is clear that the incidence of radiocontrast acute renal failure in diabetic patients rises sharply as the baseline serum creatinine rises. Diabetic patients with a serum creatinine value greater than 1.5 mg/dl have an approximately 50% chance of developing acute renal failure (11,28). Harkonen and Kjellstrand (11) reported that 22 of 29 or 76% of all diabetic patients with a serum creatinine greater than 2 mg/dl developed acute renal failure following intravenous pyelography. Diabetic patients with a baseline serum creatinine over 5 mg/dl and those developing diabetes before the age of 40 years had an even greater risk of acute renal failure. In 56% of these later patients, acute renal failure was irreversible. The experience of 13 patients with juvenile-onset diabetes with advanced diabetic nephropathy (mean serum creatinine of 6.8 mg/dl) undergoing coronary angiography was equally stark with 12 of 13 or 92% developing acute renal failure (32). The age of onset of diabetes also seems to affect the severity and likelihood of developing radiocontrast acute renal failure. Type II diabetics are less likely to develop radiocontrast induced acute renal failure than Type I diabetics (11,52). Nonetheless, the risk of developing acute renal failure in Type II diabetics is not trivial. Shieh et al (52) reported a 6% incidence of acute renal failure after excretory urography in 49 type II diabetics who as a group had only minor renal impairment (mean baseline serum creatinine, 1.3 mg/dl and mean creatinine clearance of 79.6 ml/min). Why these diabetic patients with near normal renal function were at a higher risk for acute renal failure is unclear. In addition to the reasons cited above that may predispose patients with renal insufficiency to further injury, diabetic patients may have as contributing factors increased blood viscosity, post capillary hypoxia with formation of microthrombi, and altered red cell deformability (38). Atherosclerosis, hypertension, and the potential role of glomerulosclerosis induced by hyperfiltration of the nephron, as demonstrated in both human and animal forms of diabetes, also could be involved.

Multiple myeloma has for many years been singled out as a high risk state for the development of acute renal failure following radiocontrast (38-41). Despite numerous case reports documenting this complication, the overall risk of developing acute renal failure is still relatively small. Retrospective studies of the incidence of acute renal failure in multiple myeloma revealed only 2 cases developing after 376 examinations (31,40,53). In the experimental animal, administration of meglumine diatrizoate

further enhances the nephrotoxicity of Bence Jones protein when the latter is given in the presence of an acid urine (54). Although the results of this animal study may not directly apply to man, it seems prudent in patients with unexplained renal disease undergoing urography or arteriography, particularly the elderly patient, to screen the urine for Bence-Jones proteins with p-toluene sulfonic acid (TSA), or if unavailable, the dipstix and sulfosalicylic acid (SSA) test (55). A positive TSA test or a negative dipstix (albumin) and positive SSA (all urinary proteins) may be considered presumptive evidence of Bence-Jones proteinuria and radiocontrast studies should then only be undertaken with extreme caution if no alternative imaging procedure is suitable. However, in the absence of proteinuria, the patient with multiple myeloma and normal renal function does not appear to have an enhanced risk of developing contrast-induced acute renal failure.

Clinical features

Radiocontrast induced acute renal failure has been reported following virtually every radiographic procedure (Table 4). The list includes excretory urography (15,17,28,35,37,48), coronary angiography

Table 4

Radiocontrast-induced acute renal failure
Type of procedure

1. Excretory urography
2. Coronary angiography
3. Aortography
4. Cerebral angiography
5. Pulmonary angiography
6. Peripheral angiography
7. Computerized tomography
8. Percutaneous cholangiography
9. Intravenous cholangiography
10. Oral cholecystography

(10,15,25,32,42), aortography (9,14,15,25,42,56), cerebral angiography (9,57,58), pulmonary angiography (15) peripheral angiography (14,15), computerized tomography of the head (15), percutaneous cholangiography (16,59), intravenous cholangiography (25), and oral cholecystography (25,60-64). Renal toxicity appears to be favored in the presence of liver disease or excessive dosages (3,42,59,61). Since the liver and kidney represent major excretory pathways for oral cholecystographic agents, reduced hepatic conjugation and excretion obligates a larger fraction to renal excretion.

Radiocontrast induced acute renal failure may be oliguric or non-oliguric. Non-oliguric acute renal failure seems to be more common in patients initially having a lower serum creatinine prior

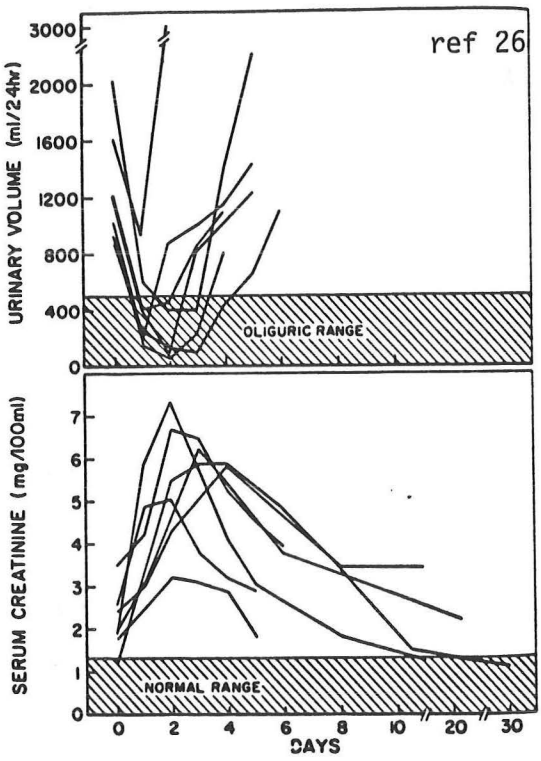


Figure 4

to receiving the contrast. The time course of the oliguria and the rise in serum creatinine depends on the baseline serum creatinine prior to receiving the contrast agent. Patients with normal or mild renal functional impairment prior to receiving radiocontrast agents usually have oliguria lasting 2-5 days with recovery to baseline urine volumes and serum creatinine by the seventh day (Figure 4). When more serious impairment of underlying renal function is present, recovery may be prolonged and require hemodialysis. Occasionally renal failure is irreversible and requires long term hemodialysis (9-11,14,27,32).

Diagnosis

The diagnosis of radiocontrast-induced acute renal failure is occasionally made when oliguria develops 24-48 hours following a radiocontrast study (Table 5). More often, a subtle, non-oliguric episode of acute renal failure is diagnosed in retrospect by

Table 5
Radiocontrast-induced acute renal failure
Diagnosis

1. Oliguria
2. Rising serum creatinine
3. Low fractional excretion of sodium (FENa)
4. Abnormal urinalysis
5. Persistent nephrogram

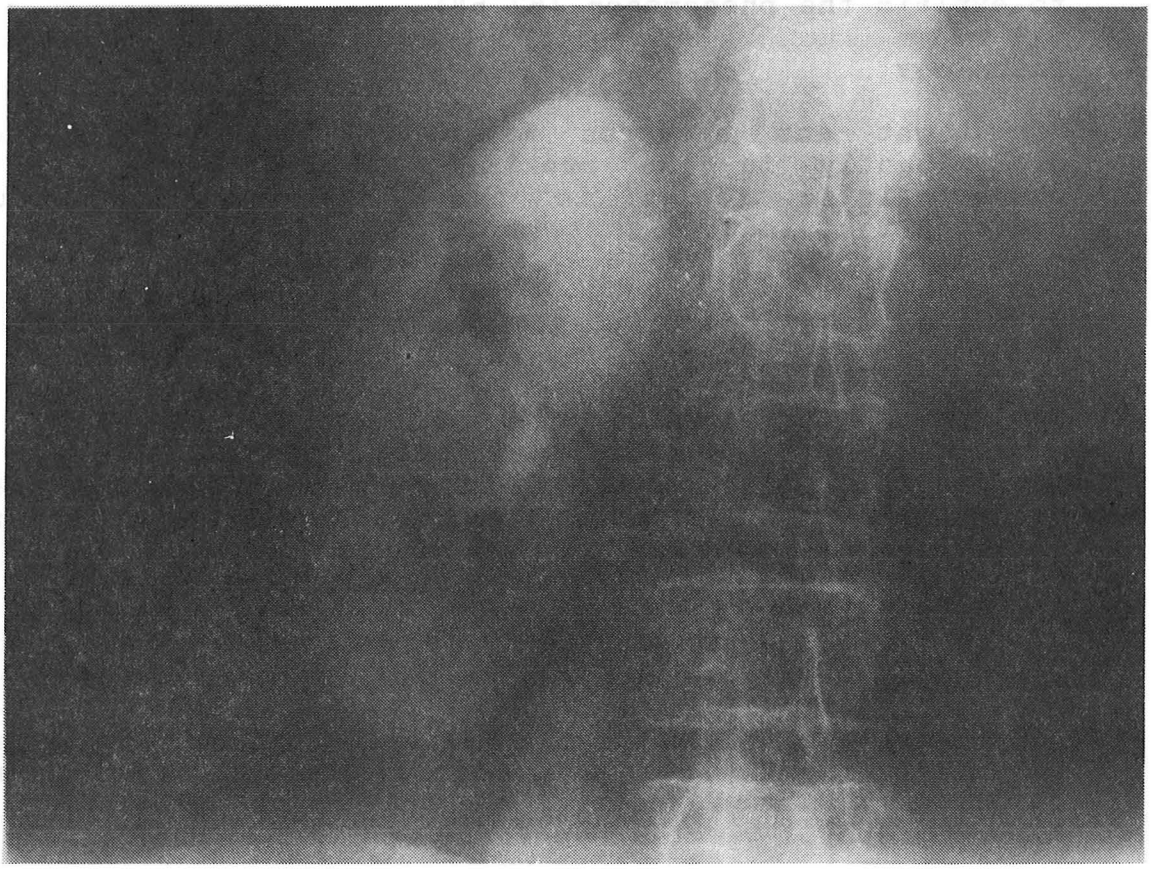
demonstrating a reversible 0.5-3.0 mg/dl rise in serum creatinine. One feature that may help distinguish radiocontrast from other causes of acute renal failure is the paradoxical and as yet poorly explained propensity for the urinary sodium concentration and the fractional excretion of sodium to be low (17,28,30,65). Carvallo et al (17) observed that 3 of 10 patients developing radiocontrast-induced acute renal failure after drip infusion pyelography had a low urinary sodium concentration (mean 7 meq/L). Fang et al (30) reported 12 patients with radiocontrast induced acute renal failure

who had a low fractional excretion of sodium (mean 0.36%) which persisted for up to 5 days during the oliguric phase. The mechanism of the low fractional excretion of sodium is unknown, but reduced renal perfusion or acute tubular obstruction have been offered as explanations (30).

The urinalysis in this disorder may show features compatible with acute renal failure (renal tubular epithelial cell casts or coarsely granular crown casts), but these changes may be absent in the presence of a functional abnormality (9). In 3 diabetic patients with angiography-induced acute renal failure, the urinary sediment showed an increase in renal tubular epithelial cells with epithelial cell casts or muddy brown coarsely granular renal failure casts, or both (32). Conversely, in the absence of demonstrable nephrotoxicity by functional criteria, radiocontrast agents may alter the urinary sediment . Gelman et al (66) demonstrated more formed elements (cells, casts, and debris) in the urine of 12 of 14 patients following angiography although none of the patients experienced a reduction in glomerular filtration rate. All patients showed amorphous urate crystals and two patients had a heavy shower of calcium oxalate crystals.

A persistent nephrogram 24-48 hours after the contrast study is a characteristic but not pathognomonic feature of radiocontrast induced acute renal failure (8,9,61) (Figure 5). In the normal subject given a bolus of radiocontrast material, renal

Fig. 5



opacification is the most dense immediately after the end of the injection and then fades rapidly with very little nephrogram effect detectable by 6 hours (67). In most patients with radiocontrast-induced acute renal failure as well as in patients with other forms of acute renal failure, the nephrogram develops quickly but fails to disappear with time. The frequency of this finding was studied by D'Elia et al (9) who performed a radiographic abdominal flat plate in patients 24 hours following angiography. They found a persistent nephrogram to be a sensitive indicator of the presence of renal failure (83% of patients with renal failure had a positive nephrogram) with high specificity (93% of patients without renal failure lacked the persistent nephrogram). Unfortunately, a high false positive rate made the predictive accuracy of a persistent nephrogram a low 19%. Thus, if a persistent nephrogram is not present this virtually excludes the presence of radiocontrast-induced acute renal failure, but its presence is of little help in predicting whether renal function will be impaired. For most clinical situations the serum creatinine will remain the most practical test for diagnosing radiocontrast-induced acute renal failure.

In experimental acute renal failure in the rat, administration of radiocontrast material leads to the same persistent nephrographic pattern that is observed in patients with acute renal failure, but these studies have not provided a plausible mechanism to explain the phenomenon (67,68).

Pathology

Light and electron microscopy (EM) show abnormalities predominantly in the proximal tubule (Table 6) (69). The characteristic lesion in the kidneys of individuals with radiocontrast-induced acute renal failure is an intense

Table 6
Radiocontrast-induced acute renal failure
Pathology

1. Swelling of kidneys
2. Focal dilatation of tubules
3. Focal or diffuse coarse vacuolizations of the proximal tubule cells, "osmotic nephrosis"
4. Focal proximal tubule necrosis
5. Hydropic swelling and focal necrosis of mitochondria (EM)
6. Cytoplasmic vacuoles and lamellated myelin bodies (EM)

vacuolization of proximal tubular cells called "osmotic nephrosis" (70,71). Moreau et al (70) described their findings from 211 renal biopsies obtained within 10 days of urography or renal arteriography. Osmotic nephrosis was found in 47 of the biopsies;

a diffuse form was found in patients with severe preexisting renal disease, while a milder focal form was seen in patients with less severe renal impairment or in patients with previously normal kidneys. However, the presence of the focal or even the diffuse form of osmotic nephrosis did not necessarily predict the presence of renal functional impairment. Conversely, virtually normal proximal tubular cells were found in patients who developed oligo-anuric acute renal failure after urography. Hyperosmolality does not seem to be required for the development of these lesions since even the newer low-osmotic contrast media are capable of inducing it (72,73). Notably, in 13 patients with histologically normal kidney, vacuoles were not found in any of the tubular cells, implying that an underlying nephropathy was required to induce this histological lesion. Moreau has suggested that the vacuoles represent molecules of the contrast medium that have entered the cytoplasm by endocytosis. However, a recent report by Heyman et al (74) (Figure 6) suggests that the origin of the vacuoles is not

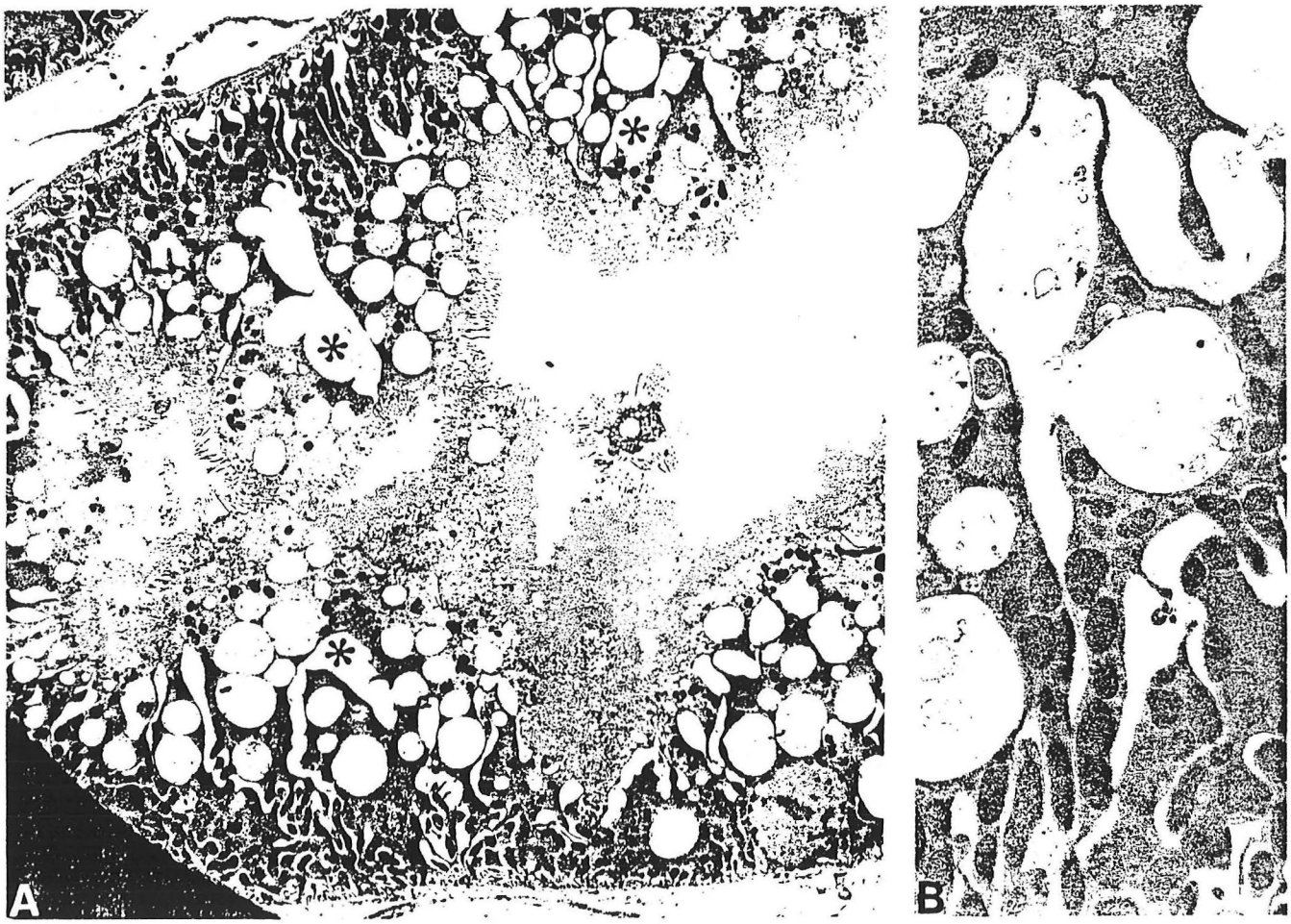


Figure 6 Salt-depleted uninephrectomized rats given indomethacin and sodium iothalamate (killed at 120 min). Low-power electron micrograph shows the extensive vacuolar formation in this proximal convoluted tubule. Although some may be of endocytotic origin, connections between the basal lateral membranes and these vacuoles are readily apparent (*). At higher power, outpouchings from these membranes are evident. ×3,600, *A;* ×11,400, *B.* ref 74

from endocytosis, but from invaginations of membranes of lateral cellular interdigitations. They suggested that the contrast media in the paracellular space may have damaged these membranes leading to the vesicular outpouchings. The presence of iodine in these vacuoles cannot be demonstrated using several techniques (74,75).

Pathogenesis

In view of the wealth of clinical descriptions of radiocontrast-induced acute renal failure, it is surprising that relatively little is known about the pathogenesis of the renal injury. Unlike other nephrotoxic substances, radiocontrast seems only to be nephrotoxic in humans. The lack of a good experimental model of radiocontrast-induced acute renal failure has slowed our understanding of its pathogenesis. Neither the normal rabbit nor the normal rat kidney is particularly susceptible to renal functional injury, although other properties of radiocontrast agents have been successfully studied in these species (71,74,76).

The observations that radiocontrast agents seem to be only nephrotoxic in compromised kidneys suggests that an impaired cell is required for development of acute renal failure (74,76). The report of a 57 year-old man with acute rhabdomyolysis who only developed acute renal failure after undergoing drip infusion urography prior to renal biopsy suggests that the underlying renal impairment need not be chronic nor severe to predispose to radiocontrast acute renal failure (27).

The currently used group of ionic radiocontrast agents were introduced about 40 years ago (Table 7). They are tri-iodinated

Table 7
Ionic Radiocontrast Agents

1. 28-37% Iodine.
2. Osm 1400-1700
3. 99.9% ionized
4. Low membrane permeability
5. Volume distribution: 20-22%
6. Excretion: glomerular filtration

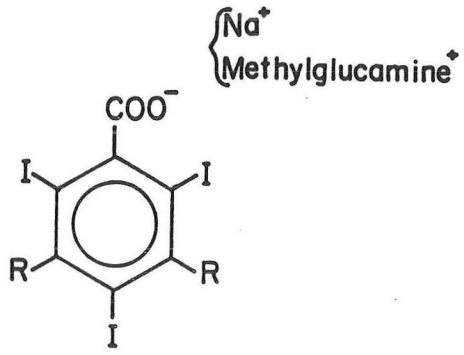


Figure 7

benzoic acid derivatives and are formulated as either the sodium or methylglucamine (meglumine) salts of diatrizoate or iothalamate (Figure 7). The efficacy of these agents for radiocontrast studies is dependent on their iodine content which ranges from 28-37% by weight. The osmolality of the different preparations ranges between 1400-1700 mOsm/kg.

There is little biotransformation of the ionic radiocontrast agents. At physiologic pH they are highly stable and greater than 99.9% ionized. Their low pKa, highly ionized form, and polar nature generally do not allow them to cross cell membranes. In man, the volume of distribution of the tri-iodinated radiocontrast agents is 20-22%, quite similar to the volume of distribution for inulin (78). This indicates that the radiocontrast agents are largely confined to the extracellular compartment. Following injection, radiocontrast agents are eliminated in 5-6 hours. More than 90% of a given dose of currently used urographic and angiographic contrast media is normally excreted through the kidneys. Clearance studies with most of the commonly used radiocontrast agents indicate that they are excreted by glomerular filtration and undergo no significant tubular secretion or reabsorption (78-80). However, hypaque may be an exception with one report indicating that 20% of filtered hypaque is reabsorbed (81). Studies in man (82) and dog (83) of the new nonionic agent metrizamide, indicate substantial reabsorption with a fractional excretion compared to inulin of 70%. The cholecystographic agents, in comparison to the urographic and arteriographic agents, are more completely metabolized and in addition are highly protein bound.

The pathogenesis of radiocontrast-induced acute renal failure is unknown, but a number of factors have been implicated (Table 8).

Table 8

Radiocontrast-induced ARF
Possible pathogenetic factors

1. Hemodynamic changes
2. Osmolality
3. Proteinuria
4. Tubular obstruction
5. Allergic and immunologic reactions
6. Enzymuria
7. Direct toxicity
8. Altered glomerular permeability

Hemodynamic Changes There are several reasons to believe that hemodynamic factors may be involved in the pathogenesis of radiocontrast-induced acute renal failure (Table 9). When radiocontrast is injected directly into the renal artery, glomerular filtration rate is reduced and there is a prolonged

Table 9

Radiocontrast agents
Hemodynamic effects

1. Initial vasodilatation
2. Prolonged vasoconstriction

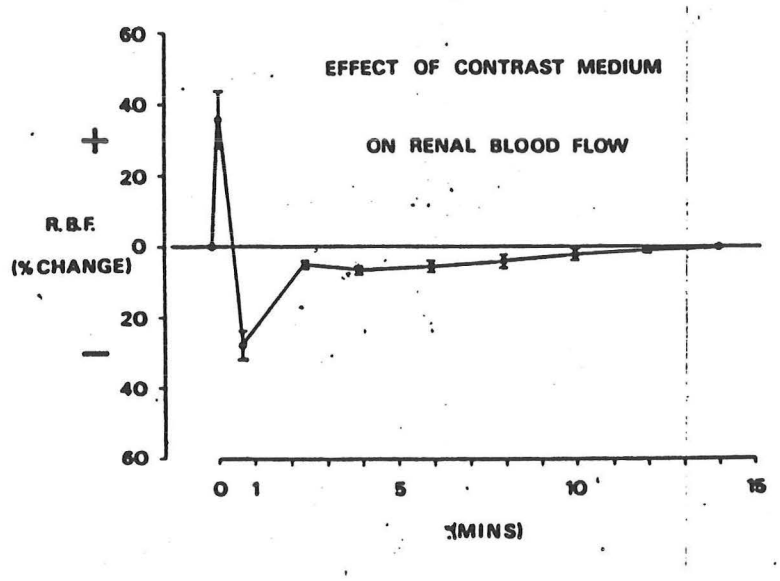
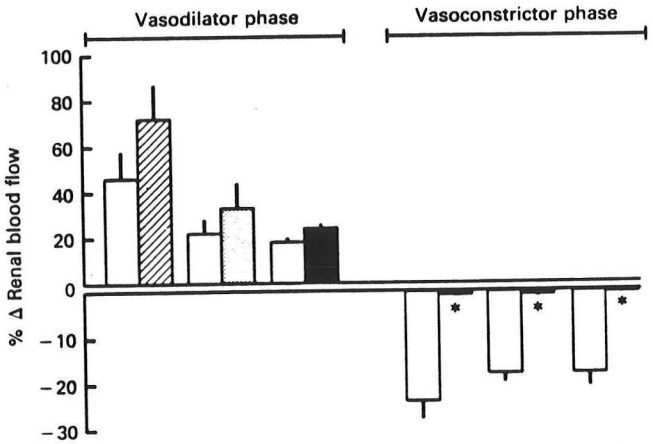


Figure 8

vasoconstriction phase (84-88). Caldicott demonstrated that intrarenally injected contrast in the dog produced a characteristic biphasic response with an initial vasodilatation, which is common to all vascular beds, followed by vasoconstriction, a characteristic only found in the kidney (Figure 8). They gave evidence that the vasoconstriction was mediated by angiotensin II. Porter et al (87) demonstrated that iothalamate injected into the left ventricle of the dog, increased cardiac output and decreased renal blood flow by 25%. When isosomolar quantities of mannitol were injected, however, the same increase in cardiac output occurred, but renal blood flow increased. In man, transient decreases in renal plasma flow and glomerular filtration rate occur after large dose excretory urography (80,89,90). However, this effect is not unique to radiocontrast agents; noncontrast hypertonic solutions also produce it (91). The response is biphasic showing initially a transient increase in renal blood flow followed by a more prolonged 10-20% decrease which may persist for up to an hour. This vasoconstrictor response of the kidney seems to be unique among the vascular beds, since it follows an initial renal vasodilatation, the characteristic and sole response of other vascular beds during the administration of radiocontrast material (15,92,93). The vasoconstrictor effect of radiocontrast cannot be blocked with alpha receptor antagonists or by blockade of the renin-angiotensin system (85,94). The vasoconstrictor but not the vasodilator effect of radiocontrast material appears to be a calcium dependent phenomenon, since the calcium channel blockers verapamil and diltiazem and the calcium chelator EGTA all can significantly attenuate the magnitude and duration of radiocontrast induced



Effects of radiocontrast medium administration on renal blood flow responses in the presence and absence of verapamil, diltiazem, and and EGTA. Symbols are: □, control; ▨, verapamil (N = 6); ⊡, diltiazem (N = 6); ■, EGTA (N = 5); *, $P < 0.05$. ref 84

Figure 9

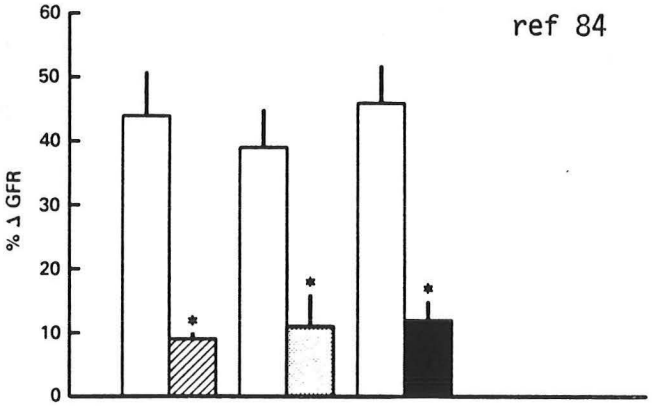


Fig. 2. *Effects of radiocontrast medium administration on glomerular filtration rate in the presence and absence of verapamil, diltiazem, and EGTA.* Symbols are: □, control; ▨, verapamil (N = 5); ⊡, diltiazem (N = 5); ■, EGTA (N = 5); *, $P < 0.05$.

Figure 10

intrarenal vasoconstriction (Figure 9) as well as attenuate the transient radiocontrast induced reduction in glomerular filtration rate (84) (Figure 10). Although calcium entry blockers block this contrast-induced vasoconstriction, an uncontrolled, retrospective analysis of patients with renal insufficiency who were concomitantly receiving nifedipine at the time they received intravascular radiocontrast did not show any protective effect against the development of acute renal failure when compared to a control group not receiving nifedipine (95).

Osmolality. Byrd and Sherman (15) reported an almost 4 fold greater chance of developing acute renal failure after intraarterial compared to intravenous administration of radiocontrast. The effect of radiocontrast agents injected intraarterially on renal vascular resistance could be directly related to the osmolality of the solution. Radiocontrast agents with a high osmolality impair renal blood flow much more than those of lower osmolality (96,97). Impaired microcirculatory flow also

occurs following injection of contrast material (98-100) and in some instances following the injection of large doses of ionic contrast material into the renal artery, kidney opacification is patchy (101). The mechanism for this decrease in flow may involve blood sludging resulting from alterations in red cell shape or loss of deformability (50,100,102,103), increased blood viscosity (100), reduced platelet aggregation (104,105), vascular endothelial injury (99), and the formation of microthrombi in the renal vascular bed (101). It is possible that the osmolality of the contrast medium could be important in some of these vascular effect, since the patchy retention of contrast is not seen with the nonionic contrast agents iohexal and metrizamide (106). These observations in turn may partly explain the observations of Fajers and Gelin (107) who showed that hyperosmolar solutions aggregated red blood cells and caused necrosis of proximal tubular cells. However, the osmolality of the radiocontrast agent is not the complete answer, since the newer nonionic contrast agents, which have a much lower osmolality, cause equal degrees of ischemia in the rabbit microcirculation (98). These data on the microcirculatory effects of radiocontrast material must be tempered by the fact that most of these observations regarding the radiocontrast-induced changes in red blood cells and platelets were made using radiocontrast concentrations far higher than those encountered clinically. Thus, the effect of radiocontrast material on these systems may represent minor effects under usual circumstances.

While the hypertonicity of radiocontrast materials injected into the renal artery clearly may have a significant although temporary effect on renal vascular resistance, it is less clear that intravenously injected contrast material that is rapidly diluted by venous blood before it reaches the kidney has an important osmolality related effect on renal vascular resistance. The importance of the injection site of the radiocontrast agents on the osmolality experience by renal vasculature was shown by Becker et al (108) who demonstrated a maximum 2.2% increase in plasma osmolality immediately upon completion of a high dose (300 ml) intravenous injection of standard ionic tri-iodinated radiocontrast agent. Moreover, more than half of the reported cases of radiocontrast-induced acute renal failure have been reported following excretory urography in which the contrast media is injected intravenously rather than intraarterially. Thus, while theoretically an attractive candidate to explain radiocontrast nephrotoxicity, the hypertonicity of these agents is unlikely to be the sole mediator of renal damage. Heyman et al (74) demonstrated selective medullary thick ascending limb (mTAL) damage in uninephrectomized, salt-depleted rats injected with indomethacin 24 hours after the administration of sodium iothalamate (Table 10). The fraction of severely damaged mTALs correlated with the rise in plasma creatinine. Except for an increase in vacuoles, proximal

Table 10

Radiocontrast-induced ARF in uninephrectomized rats

Experimental Group	Plasma Creatinine µmol/L		Proportion of mTALs collapsed %	necrosis
	Day 0	Day 1		
Salt depleted + CM	107±14	97±3	60±14	0
Indomethacin + CM	117±11	113±14	62±12	9±3
SD+Indo+CM	103±3	211±22*	33±8	30±7
SD+Indo	101±12	151±24	26±16	9±8

*p<0.001. SD=salt depleted. Indo=indomethacin. CM=contrast media

ref. 74

convoluted tubular cells were not injured. Since mTALs are a very active high oxygen dependent transporting epithelium, these findings suggested that the radiocontrast agent mediated renal failure in some way by causing hypoxia of the renal medulla, an area of the kidney which normally has only a meager blood supply. Supporting this thesis was the further demonstration in isolated perfused kidneys that contrast-induced mTAL injury was almost completely eliminated by inhibiting sodium transport in this segment with ouabain.

Proteinuria. Radiocontrast agents injected intraarterially also have a profound but short lived effect on glomerular permeability to proteins. Nephroangiography is associated with transient, but massive proteinuria in man (109) and the dog (83,110,111). Holtas (83,110,111) found that injection of contrast media into the renal artery produced albuminuria that peaked 45 minutes after injection. Here also the adverse effect was independent of the osmolality of the agent employed, since both ionic and non-ionic compounds caused the same relative increase in albuminuria. This suggested that it was rather a property of the molecule rather than the osmolality of the solution that caused the increase in glomerular permeability. Massive proteinuria only occurs when the glomerulus is directly exposed to high concentrations of the contrast agent during angiography. Only relatively minor proteinuria, 1/300 of that found after angiography, occurred in dogs given intravenous contrast (110). The mechanism involved in this transient loss of the glomerular capillary barrier to the movement of large molecular species is unknown, but may be analogous to the temporary opening of the blood brain barrier which occurs following radiocontrast injection into the cerebral circulation (112).

Tubular obstruction. The pathological hallmark of myeloma kidney is intratubular casts (113,114). The associated renal functional impairment is felt to be at least partly due to tubular obstruction. Such observations suggest that contrast agents may accelerate the precipitation of Bence-Jones proteins. Lasser et al (115) demonstrated that two urographic contrast agents no longer in use because of their toxicity, iodopyracet (Diodrast) and sodium acetrizoate (Urokon), produced in vitro precipitates in the urine of myeloma patients in a pH range of 4.5-5.5. However, agents that have been in use for the last 25-30 years, meglumine diatrizoate (Renografin) and sodium diatrizoate (Hypaque) did not produce precipitates in this pH range. Nevertheless, both agents are capable of causing acute renal failure in multiple myeloma (40). McQueen et al (116) demonstrated that Bence-Jones proteins readily cause Tamm Horsfall proteins to sludge in vitro. Whether this same phenomenon occurs in vivo and causes tubular obstruction as proposed by Berdon et al (38) is still unknown.

The uricosuric property of radiocontrast agents led to the theory that intratubular obstruction might occur from uric acid crystallization in the nephron (47,117). The oral cholecystographic agents (Telepaque, Oragrafin, and Cholografin) are the agents most often reported to cause uricosuria, but Hypaque to some degree also shares this property (117). Urinary uric acid measurements before and after contrast have been reported in one patient who developed acute renal failure (118). Acute renal failure occurred despite a 3 week course of allopurinol and in the absence of any uricosuric effect in the 6 hours following diatrizoate injection. In normal individuals a prompt increase in urinary oxalate excretion occurs following diatrizoate injection (66). Whether enhanced oxalate excretion is a factor in tubular obstruction is unknown.

Based on these limited data, it seems unlikely that acute urate nephropathy or enhanced oxalate excretion is a major factor in the pathogenesis of contrast-induced acute renal failure.

Allergic and Immunologic radiocontrast reactions. Radiocontrast agents may cause acute allergic reactions and even anaphylaxis leading to death (119). The mechanisms by which this happens are not clear, but radiocontrast agents stimulate histamine release and increase microvascular reactivity, factors which could be participants in both the allergic reactions as well as in the production of acute renal failure. Ring et al (120) demonstrated that the infusion of radiocontrast material into the rabbit led to a dose dependent change in systemic arterial pressure, microvascular pressure, and red blood cell volume. In addition, radiocontrast material led to a marked rise in histamine release and a reduction in complement (CH_{50}). Although the initial hemodynamic changes could be mimicked by hypertonic saline, it had only a trivial stimulatory effect on histamine release and had no effect on complement levels. Also, the effects of radiocontrast agents on systemic hemodynamic changes were not as quickly reversible as were those of saline. There are other areas where

immunologic and hemodynamic disturbances caused by radiocontrast could potentially overlap in producing acute renal failure. Human studies have demonstrated that radiocontrast agents in vitro cause serotonin release (121), impaired platelet function (122), and stimulate the formation of fibrin split products (123).

IgM kappa type antibodies against contrast material have been detected in a patient who developed acute renal failure following her first exposure to radiocontrast during excretion urography (124). Radiocontrast material, injected either intravenously or intraarterially, have been implicated in renal transplant rejection (49,50). While radiocontrast agents can clearly cause induction of antibodies (122), how these antibodies might lead to acute renal failure is not known.

Enzymuria. Radiocontrast agents cause a marked, but short-lived increase in the urinary excretion of a variety of brush border enzymes, a finding indicative of injury to proximal tubular cells (69,125). Peak output of these enzymes usually occurs 24-48 hours post-angiography with values then returning quickly to normal. Hartmann et al (69) angiographically studied 20 patients with benign essential hypertension without evidence of renal insufficiency (endogenous creatinine clearance greater than 80 ml/min). All patients had increases in urinary enzyme excretion, but the magnitude and pattern varied among the individual patients (Figure 11). Despite the enzyme changes there were no parallel changes in creatinine clearance. The greatest rise in enzyme activity for the group occurred in alkaline phosphatase, which rose 428%. Whether this increase in enzyme activity in the urine following angiography in fact represented tubular injury was unclear. The suddenness with which enzymuria develops and its rapid reversibility suggests that tubular damage is minimal.

Since hypertonic mannitol and hypertonic saline also produce significant increases in enzymuria (LDH, SGOT, CPK, catalase), it is possible that hypertonicity rather than a direct effect of the contrast agent is the cause of the enzymuria (126). However, in the dog the degree of glomerular proteinuria produced by contrast is 100-fold higher

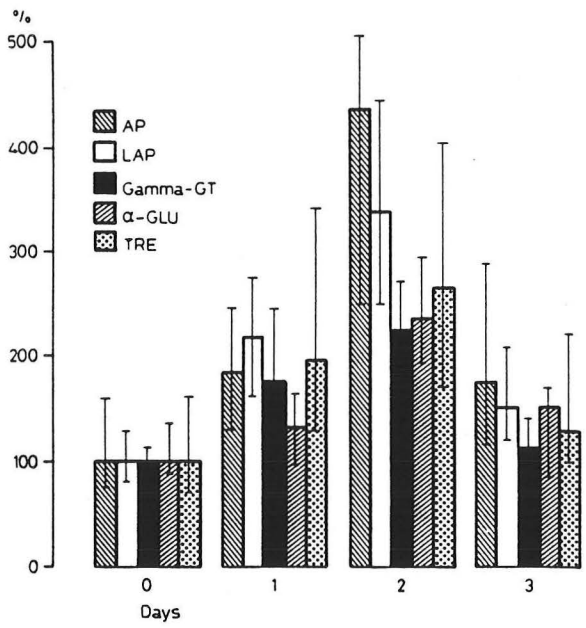


fig 11 Quantitative measurements of the excretion of the brush-border enzymes AP, LAP, gamma-GT, α-GLU and TRE in 24-hour urine samples collected before angiography (day 0), on the day of angiography (day 1) and on the 1st and 2nd days after angiography (days 2 and 3). The results are expressed as percentages of the initial value (day 0 = 100%). ref 69

than that resulting from equally hypertonic saline (110). Clearly, other factors are also important.

Direct toxicity. A direct nephrotoxic effect of radiocontrast material on tubular cells is the most widely held theory to explain radiocontrast-induced acute renal failure. Diatrizoate and iothalamate both have been shown to alter tubular transport of sodium (87,127,128). Cunningham et al (127), demonstrated that radiocontrast agents induced more of a diuresis and natriuresis than equiosmolar mannitol and that the diuresis occurred within 3 minutes of injection. Ziegler et al (128) demonstrated that radiocontrast agents had an inhibitory effect on sodium transport in toad bladders when used in isotonic amounts, (Figure 12). Interestingly, the sodium diatrizoate bladder was still responsive to the action of antidiuretic hormone and the effect on sodium transport was reversible when the contrast agent was washed out. The serosal side of the bladder, analogous to the basolateral or contraluminal aspect of nephronal cells was more sensitive to the adverse effects. This is of particular interest in view of the histologic observations of osmotic nephrosis in man which has focused attention on the abnormalities occurring at the luminal surface of proximal tubular cells. While the mechanism of reduced sodium transport is not clear, an inhibition of Na,K-ATPase in the basolateral membrane of the toad bladder cells or a direct effect on energy production has been postulated (128). Although these effects of radiocontrast on sodium transport do not necessarily indicate cellular injury or toxicity, they represent one of the few demonstrations that radiocontrast agents at isotonic concentrations have a direct cellular inhibitory effect apart from hemodynamic effects. Lastly, in the isolated perfused kidney model of contrast-induced acute renal failure, histologic damage to medullary thick ascending limb cells was markedly reduced when the kidney was in the non-filtering mode (74). This suggested that injury to these medullary structures depended on the intraluminal presence of the contrast material.

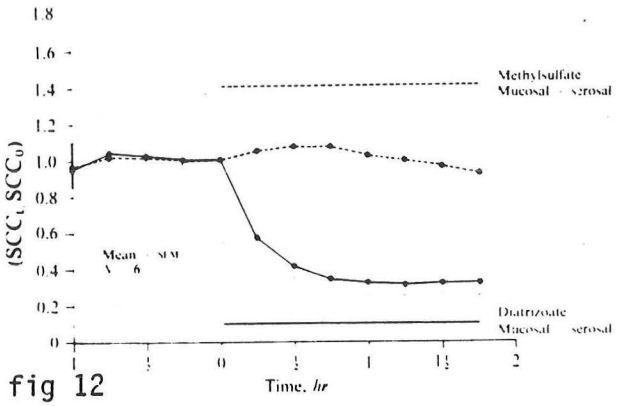


fig 12

Comparison of the effects of sodium diatrizoate and sodium methylsulfate. These compounds were added at 78 mM to both mucosal and serosal solutions at time zero. The absolute SCC at time zero for the diatrizoate-treated group was 161 ± 37, and for the methylsulfate-treated group, 147 ± 28 μA 3.37 cm² (mean ± SEM).

ref 128

Several observations from clinical and experimental studies suggest that radiocontrast agent nephrotoxicity is determined by the anionic portion of the molecule. Both sodium acetrizoate and sodium diatrizoate have the same cation and the same number of iodine atoms per molecule, but sodium acetrizoate is no longer used due to its high incidence of nephrotoxicity. Although the precise reason for the different nephrotoxicities of these two

radiocontrast agents is not known, several observations suggest that a difference in access to the interior of proximal tubular cells may explain nephrotoxicity. The renal clearance of acetrizoate in man is 600 ml/min indicating a substantial component of tubular secretion (129). Also, sodium acetrizoate reduces the tubular secretion of p-aminohippurate, further evidence that this particular radiocontrast agent is transported into the cell along the organic acid secretory pathway (130). On the other hand, the renal handling of iothalamate, an example of the currently used tri-iodinated compounds, in man has a renal clearance identical with that of inulin (131), implying neither secretion nor reabsorption. However, another agent from this group, sodium diatrizoate has been shown to undergo both tubular secretion and tubular reabsorption (80,81).

For nephrotoxicity to occur with the currently used agents, it is probably that some of the radiocontrast gains access to the cell interior. Humes et al (132) using isolated renal proximal tubule cells showed that diatrizoate sodium, and to a lesser degree meglumine, is directly toxic (Table 11). Diatrizoate when incubated with these tubules for 97 minutes

Table 11

Effect of <u>in vitro</u> diatrizoate on renal proximal tubules

1. Decreased tubular K^+ content
2. Decreased tubular ATP
3. Decreased basal and uncoupled tubule respiratory rate
4. Increased tubule Ca^{++} content
5. Hypoxia augmented effect
6. Threshold dose 1-10 mM

ref 132

produced a significant decline in tubule content of K^+ and ATP, a significant decrease in basal and uncoupled tubule respiratory rate, and a significant increase in tubule content of Ca^{++}. The threshold dose for the diatrizoate effect was between 1 and 10 mM, a concentration range that is achievable in clinical practice (132). The study also demonstrated that combining hypoxia with diatrizoate led to additional injury. When viewed together with the inherent vasoconstrictive properties of radiocontrast agents, these findings may explain why certain clinical states often associated with relative renal ischemia (volume depletion, prior renovascular disease) are more often associated with radiocontrast-induced acute renal failure. The finding that contrast media enhances mTAL injury in the isolated perfused kidney, an experimental model which is inherently hypoxic under the best of circumstances, supports this <u>in vitro</u> study (74).

Lasser et al (133) studied the histologic effect of several

contrast agents injected directly into the dog kidney. The halogen moiety of the molecule appeared to be the toxic portion, since injection of the basic non-halogenated molecule constructed with prosthetic groups on all position on the benzene ring caused little renal histologic damage. Iodinated contrast agents are usually quite stable at normal body pH, but some deiodination does occur in vivo (134-136). After urography or cholecystography, blood iodide may be elevated up to 200-fold for several days (137,138). The fractional excretion of ^{131}I is approximately 40%, indicating significant tubular reabsorption of the free iodide molecule (139). Older cholecystographic agents which caused acute renal failure commonly released substantial free iodine into the circulation and levels remained above normal for up to 5 days (140). Protein bound iodine remained high for many months. Also, as much as 5 mg of free iodine per dose may be present as a contaminant in urography dyes (141,142). Whether these temporary elevations in iodide levels are nephrotoxic to normal or impaired proximal tubular cells is unclear. Whether renal cortical levels of radiocontrast are high after exposure is also. Moreau et al (75) were unsuccessful in attempts at demonstrating iodine atoms in renal biopsies of patients with osmotic nephrosis. Similarly, electron probe microanalysis was unable to demonstrate iodine in rat kidneys following the administration of radiocontrast (74).

In a normal individual, the usual contrast load is probably handled with minor impairment of normal cellular function. Enzymuria might be considered a marker of such transient tubular injury. However, in the presence of chronic disease characterized by sublethal cellular dysfunction, the added stress of a contrast and/or iodine load might precipitate cellular death. Many questions are left unanswered when examining the problem of radiocontrast-induced acute renal failure. The transient nature of the effect of radiocontrast material on renal blood flow and glomerular filtration rate do not suggest that these are primary mechanisms leading to acute renal failure. Toad bladder studies showing impairment of sodium transport raise the possibility that radiocontrast agents may impair sodium transport, possibly by inhibiting the enzyme Na,K-ATPase (128).

It is even more difficult to correlate the clinical risk factors with the clinical and animal studies described previously. The increased incidence of radiocontrast-induced acute renal failure in older patients may just reflect an increased likelihood for such patients to have vascular disease and renal impairment. Renal insufficiency is also very prevalent in patients with diabetes who develop radiocontrast-induced acute renal failure and is probably the single most important risk factor for this group. Dehydration or volume contraction has been cited as a major risk factor in patients with multiple myeloma or diabetes mellitus. Other factors such as proteinuria and hyperuricemia, are present in only some patients who develop contrast-induced acute renal failure.

Although clinical reports are conflicting on whether radiocontrast-induced acute renal failure is a dose related

phenomenon, it seems most prudent to assume that it is. There is no a priori reason to consider that this nephrotoxin is different from most others shown to be dose dependent in their toxicities. When appropriate animal models of radiocontrast nephrotoxicity are developed, it is likely that a dose response relationship will be uncovered. While there is not uniform agreement on the point (51), the clinical observation that repeated contrast studies over several days time is associated with a greater risk of nephrotoxicity suggests that total dose is important (4,5,42,45,46). These observations suggest that radiocontrast-induced acute renal failure is not an all-or-none phenomenon. Rather, mild subclinical or sublethal renal injury may only become clinically detectable after a threshold is reached or when another insult is present, e.g. hypoxia, prostaglandin inhibition (74,76,132).

Altered glomerular permeability (Figure 12-15). The experimental model of contrast induced acute renal failure that most closely approximates the abnormalities seen in man is that of Vari et al (76). These investigators consistently produced reversible acute renal failure in rabbits by placing them on a low sodium diet for 7 days, using indomethacin (18 mg/kg), and then administering contrast media (7 ml/kg). Glomerular filtration rate was not affected by the contrast material in these rabbits on the low sodium diet unless indomethacin was also given (Figure 13). Longterm DOCA but not acute saline or acute mannitol infusions prevented acute renal failure (Figure 14). Light microscopy showed no abnormalities of glomeruli or tubules, but micropuncture studies of individual nephrons showed that glomerular hydraulic conductivity, Kf, was significantly reduced during acute renal failure with no significant

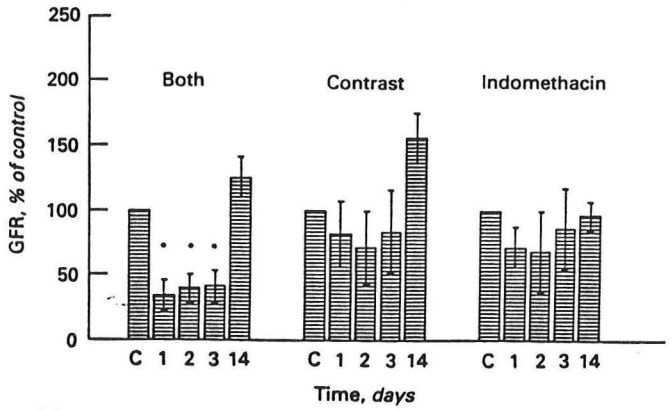


Fig. 13 *Glomerular filtration rate plotted as % of control (C) on day 1, 2, 3 and 14 following injection of contrast and indomethacin (N = 12) or contrast (N = 10) or indomethacin (N = 9).* * Significant difference vs. C. ref 76

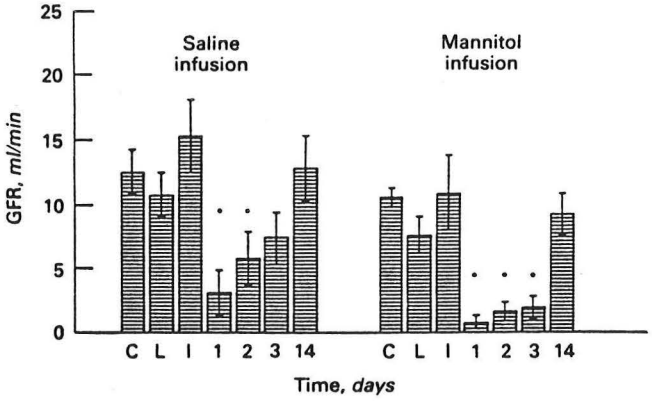


Fig. 14 *GFR in animals given either saline (N = 7) or mannitol (N = 7) infusion simultaneously with the injection of indomethacin and contrast media.* GFR is shown before (C) and 1 week after low sodium intake (L). GFR is also shown during infusion (I) and 1, 2, 3 and 14 days after infusion. * Significant difference vs. L. ref 76

increase in intratubular pressure or decrease in renal blood flow (Figure 15). Whether renin suppression or the solute diuresis resulting from the DOCA administration was a factor in protection could not be discerned from the data.

New Radiocontrast Agents

The new non-ionic and dimeric radiocontrast agents have been in use in this country for about 4 years and there has been the hope that they would be less toxic than the ionic agents (Table 12). The non-
ionic agents, unlike, for example,

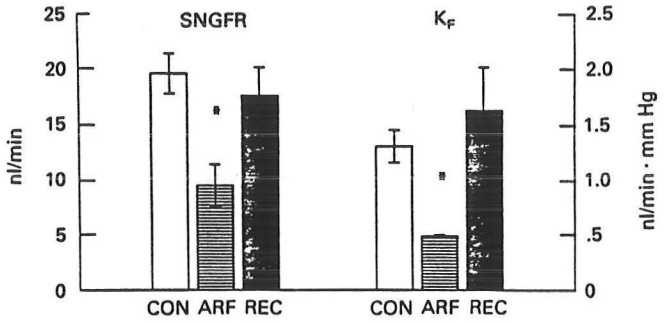


Fig. 15 *Ultrafiltration variables measured in control (N = 10), contrast media acute renal failure (N = 7) and recovery rabbits (N = 5).* SNGFR, single nephron filtration rate; Kf, glomerular ultrafiltration coefficient. * Significant difference between ARF vs. CON and REC, which were no different from each other. ref 76

Figure 15

Table 12

Comparison of ionic and nonionic agents

	Ionic	Nonionic
Iodine content	28-37%	18-38%
Osmolality	1400-1700	600-1000
% ionized	99.9	0
Membrane permeability	Low	High
Volume of distribution	20-22%	56%
Excretion	Glomerular Filtration	

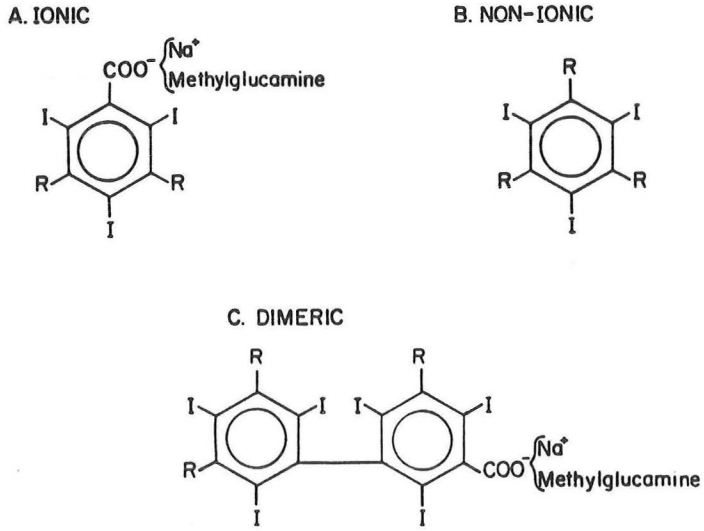


Figure 16

sodium diatrizoate, do not dissociate into anionic and cationic components upon administration and thus are only moderately hypertonic to blood (Figure 16). The dimeric compounds dissociate into an anion containing two benzene rings containing six iodine atoms and a cation of either sodium or methylglucamine. Since the iodine content of these dimeric compounds is twice that of either the ionic and non-ionic agents, similar amounts of iodine can be given with only half the osmotic load. The agents appear to be intrinsically less toxic. The median lethal dose of intravenously administered iohexol, a nonionic agent, is three times greater than that of the ionic contrast agents (143). Nonionic agents seem to have a particular advantage in several procedures (Table 13. Systemic effects such as the feeling of warmth (especially after intravenous use) which

Table 13

Procedures where nonionic agents are preferred

Procedure	Advantage
1. Myelography	-better mixing with CSF -does not need to be removed
2. Digital subtraction angiography	-less patient movement
3. Leg phlebography	-reduced volume injected -less pain
4. Coronary arteriography	-less sinoatrial depression -less conduction disturbance -less myocardial depression

depends on iodine content, osmolality, and sodium ion concentration are less with the nonionic agents (144). Despite these apparent advantages, several problems exist that will slow their acceptance into general use. The agents are difficult and expensive to manufacture and are unstable in solution. Metrizamide, for example is available only as a lyophilized preparation. This factor makes it both difficult and expensive to use. Iohexol and iopamidol are sold as liquids. Unlike the ionic agents which are minimally reabsorbed by the nephron, the non-ionic agents are to some extent reabsorbed by the proximal tubule, but there is a species specificity to the property (145). Like the ionic agents, these agents also cause proteinuria when injected directly into the renal artery, but the magnitude of this effect is less than with the ionic agents (12). The nonionic agents also have significantly less cardiac effects, causing less depression of ventricular contractility and less reduction in coronary sinus calcium concentration (144). The nonionic agents also appear to have less effect on complement consumption, cause fewer hypersensitivity

reactions, and have a less disruptive effect on the endothelial wall of blood vessels (146). In experimental animals, metrizamide is less toxic than the ionic contrast agents. The LD_{50} for mice for the ionic compounds (diatrizoate, iothalamate, metrizoate) is 8.9 grams of iodine per kilogram compared with 17.5 grams of iodine per kilogram for metrizamide. Using an in vitro preparation of rabbit renal proximal tubule cells, Messana et al (147) showed that when these renal tubules were made hypoxic, the nonionic iopamidol caused loss of cellular potassium and impaired basal and uncoupled respiration rates less than diatrizoate under the same conditions. Based on the favorable clinical reports of less adverse reactions and better patient tolerance, the nonionic agents would seem to be the best choice. However, the cost considerations in using nonionic agents is considerable. The nonionic contrast agents causes fewer adverse reactions than ionic agents but are priced 10-20 times higher (7,148-151). Powe et al (7) prospectively examined the economic impact of using exclusively ionic contrast media in 795 high-risk inpatients undergoing diagnostic cardiac catheterization, peripheral angiography, computed tomography of the head, or computed tomography of the body (Table 14). Specifically, they measured the costs to the radiology department, the hospital, and

Table 14

Cost differential in using nonionic agents

Procedure	Added cost per procedure
Cardiac Catheterization	$179
Peripheral Angiography	$132
CT Head	$146
CT Body	$ 93

Note: Cost of treating adverse reactions from ionic agents included.

Ref. 7

the charge-paying insurers for managing adverse reactions and then compared the difference in material costs between the ionic and nonionic media. Mild reactions occurred in 45%, moderate reactions occurred in 6%, and severe reactions occurred in 0.4% of patients. The average cost to the hospital to manage the reactions was $6.00 per patient. They then analyzed the same data and assumed that the patients had received a nonionic agent and experienced no adverse effects. The cost of substituting nonionic contrast media for ionic contrast media would have added $179 for each cardiac catheterization, $132 for each peripheral angiogram, $146 for each head CT, and $93 for each body CT. Overall, the material costs were 17 higher with the nonionic agents. As a compromise position, it has been recommended that the nonionic agents be used only in

patients with chronic renal failure or diabetes mellitus (7,148). However, published data regarding toxicity of nonionic agents in these two groups does not support this recommendation. The nonionic agents are clearly capable of causing renal injury in man and their superiority over ionic agents has not yet been established. Several studies during the past few years have examined the nephrotoxicity of non-ionic contrast media (6,19,51,143,152). A few of these studies have been prospective and controlled (19,51) and in one the patients were also randomized to either the ionic or nonionic agent (6).

Gomes et al (143) examined 145 high-risk patients who underwent angiography after administration of the nonionic contrast agent iohexol and compared the incidence of renal toxicity to an historical control group of 202 high-risk patients who received ionic contrast agents (Table 15). In the ionic group of patients, 10%

Table 15

	Acute Renal Failure	Dialysis
Ionic (202)	20 (10%)	5
Nonionic (145)	8 (5.5%)	0

ref. 143

developed acute renal failure compared to 5.5% in the nonionic group. Five patients in the ionic group required dialysis therapy while none in the ionic group required dialysis. However, neither of these two differences was statistically significant. Moreau et al (71) demonstrated diffuse osmotic nephrosis in four of 33 patients given metrizamide during urography prior to renal biopsy. Two of these patients experienced acute renal failure (serum creatinine rising from 2.3 to 4.6 mg/dl and 8.3 to 16.6 mg/dl at 48 hours, respectively). Gale et al (152) found no difference in the urinary excretion of N-acetyl-β-glucosaminidase, a marker of proximal tubular injury, following iopamidol, a nonionic contrast agent, compared to either iothalamate or diatrizoate, both ionic agents. Schwab et al (6) examined the relative nephrotoxicity of iopamidol (nonionic) or diatrizoate (ionic) in patients undergoing cardiac catheterization. Patients were stratified for risk (e.g. heart failure, diabetes, renal insufficiency). Nephrotoxicity was defined as an increase in serum creatinine of 44 μmol/L (0.5 mg/dl) within 48 hours of the study. In neither the high nor the low risk group was there a significant difference in nephrotoxicity between those patients receiving ionic versus nonionic agents (Table 16)

Table 16

	Significant Rise in Serum Creatinine	
	Low risk patient	High risk patient
Diatrizoate (ionic)	10.2%	17%
Iopamidol (nonionic)	8.2%	15%

ref. 6

Further, the severity of the renal failure between the groups as judged by the level of increase of serum creatinine was not different (Figure 17). Of interest, all patients in this prospective randomized study routinely received intravenous fluids as a precaution to minimize nephrotoxicity (1-1.5L 5% dextrose in 0.45% saline prior to the study and at a rate of 125 ml/hr for four hours afterwards). Parfrey et al (19) also were unable to demonstrate a difference in nephrotoxicity in high-risk patients (e.g. renal insufficiency, diabetes), between ionic and nonionic agents.

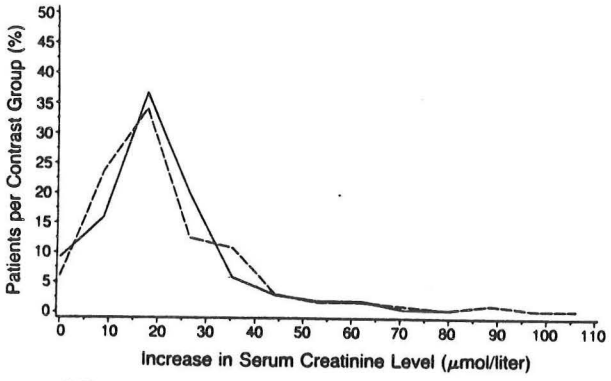


Figure 17 Peak Increases in Serum Creatinine Levels after the Administration of Contrast Agents.

The percentage of patients is plotted against the maximal increase in creatinine level from base-line values. The solid line represents 208 patients receiving iopamidol, the dashed line 235 patients receiving diatrizoate. ref 6

Prevention of Radiocontrast-induced Acute Renal Failure

In the absence of a clear understanding of the pathogenesis of radiocontrast-induced acute renal failure, guidelines for preventing this disorder must be based on the best interpretation of published clinical observations. In situations where renal function is presumed to be normal (e.g. kidney donors) there is little evidence that exposure to radiocontrast agents carries more than a 1% incidence of acute renal failure. Since renal insufficiency is indisputably a risk factor, contrast studies should be done on this background only when the results produced by the study outweigh the risk of precipitating acute renal failure. If the patient has a baseline creatinine of 5 md/dl or greater the risk of acute renal failure is high and the possibility of irreversible acute renal failure must be considered and discussed with the patient. Chronic hemodialysis is not an unusual outcome for many of these patients. Although, the roles of

hydration, volume status, dose of contrast, and concomitant nephrotoxins as risk factors are controversial, there are many historical and experimental parallels that suggest that they are factors that influence what effect radiocontrast agents will have on the kidney. A lack of consistent correlation with renal failure for each of these risk factors is more likely a fault of individual study design.

Mannitol decreased the incidence of radiocontrast-induced acute renal failure in a small group of patients when given within one hour of the radiocontrast (153,154). The precise interpretation and weight that should be given to such data is unclear, since in one report only five patients each were studied in the experimental and control group (154). Also, since radiocontrast agents promote a vigorous osmotic diuresis, the mechanism by which mannitol traditionally has been credited with protecting man and experimental animals from acute renal failure, it is unclear just how mannitol might afford protection against radiocontrast-induced acute renal failure. Other reports fail to demonstrate a protective effect from mannitol (13,155).

Similarly, furosemide has been administered prior to administration of contrast media, in the presence or absence of saline or mannitol. Here also there is little data to support the use of this drug. Table 17 shows some hydration and drug program recommendations which have been used to prevent radiocontrast-

Table 17

Precontrast Hydration Recommendations

Composition	Rate	Duration	Ref.
20% mannitol/furosemide 100 mg/mg SCr		-1h to 6h	174
0.5% saline ± mannitol ±furosemide	75 ml/h	"before and several hours afterwards"	175
saline	550 ml saline + 250 ml flush per hr during arteriogram		22
5% dextrose in 0.45 saline	1.5 L before and 125 ml/hr after x 4h		6

induced acute renal failure. Unless the patient has an underlying unstable cardiovascular system, volume expansion of every patient prior to receiving radiocontrast seems prudent and warranted. The addition of mannitol and/or furosemide to this regimen would appear to add little in the way of risk and, in experimental forms of acute renal failure, seems to have a beneficial effect.

Multiple Cholesterol Emboli Syndrome Following Angiography

CASE REPORT

H.T. is a 62 year old white male who has been followed at the Dallas VA Medical Center since 1984 for 1) hypertension, 2) coronary artery disease manifested by angina, and 3) widespread atherosclerotic vascular disease. In 1984, his blood pressure was 120/80 mm Hg and was controlled with alpha-methyldopa, 250 mg twice daily, and Dyazide, 1 tablet daily (Figure 18). Over the next 3 years the patient's blood pressure remained well-controlled even after he stopped the diuretic. In 1986 he developed intermittent anginal pains that responded to sublingual nitro-glycerine.

In November of 1987, the patient was admitted to the Ophthalmology Service at the DVAMC for a bilateral blepharoplasty and on the admission physical examination had bilateral carotid and femoral bruits and reduced peripheral pulses. Funduscopic exam revealed a yellow plaque at the bifurcation of the right inferior temporal artery. The plaque was thought to represent a cholesterol embolus. Because of this, he was electively admitted to the Vascular Surgery Service on January 2, 1988 for cerebral arteriography. Blood pressure at this time was 150/100 and his only antihypertensive medication was alpha methyldopa 250 mg four times daily. Laboratory studies showed a BUN of 13 mg/dl and serum creatinine of 1.2 mg/dl. A carotid arteriogram was performed on January 6, 1988 from a left femoral approach and demonstrated a 50% stenosis at the origin of the right common carotid artery with a slight narrowing at the origin of the right external carotid. The rest of the carotid circulation on the right was only mildly diseased. The left internal carotid was completely occluded at its origin. There was also a 50% stenosis at the origin of the left external carotid artery with no significant collateral flow from the external circulation to the cerebral circulation. The left cerebral circulation cross-filled from the anterior communicating artery. Due to the patient's lack of specific complaints and total absence of lateralizing signs, and because he did not demonstrate amaurosis fugax, operative repair was not recommended and he was discharged home. The last blood pressure in the hospital prior to discharge was 180/108. Three and one-half weeks later the patient contacted me and reported that his blood pressure at home was 218/120. Nifedipine was added to his regimen but the blood pressure continued to remain out of control. A week later minoxidil was added but the blood pressure remained elevated. In mid-February, he was admitted to a hospital near his home complaining of chest pain and headache. Blood pressure at that time was 200/120 and the laboratory studies showed a BUN of 28 mg/dl and a creatinine of 2.3 mg/dl, significantly elevated from his pre-arteriogram creatinine of 1.2 mg/dl. After 2 weeks of trying various drug combinations, his blood pressure was finally controlled at 150/80 mm Hg on verapamil 120 mg twice daily, furosemide 40 mg daily, captopril 25 mg four times daily and labetalol 200 mg twice daily. In early

April, the patient returned to the DVAMC with a blood pressure of 180/120 mm Hg and a BUN of 35 mg/dl and serum creatinine of 2.4 mg/dl. Medications were: captopril 25 mg four times daily, verapamil 120 mg twice daily, and labetalol 400 mg twice daily. A renal sonogram on 4/27/88 showed a right kidney of 9.8 cm in length and a left kidney of 10 cm. Each kidney had a solitary cyst, but the exam was otherwise normal, specifically showing no evidence of obstruction. To determine whether renovascular obstruction or occlusion might account for the sudden loss of renal function, a renal scan was performed on 5/10/88. This study showed normal symmetric blood flow bilaterally, although overall function of both kidney was felt to be depressed.

In mid-September the blood pressure was 136/86 on captopril 25 mg three times daily, labetalol 200 mg in the AM, 400 mg in the PM and verapamil 120 mg twice daily. BUN was 27 mg/dl and serum creatinine was 2.2 mg/dl. On Jan 4, 1989, the blood pressure was controlled on the same medications, but the BUN was 34 mg/dl and the creatinine was 2.2 md/dl, not significantly changed from the values in September.

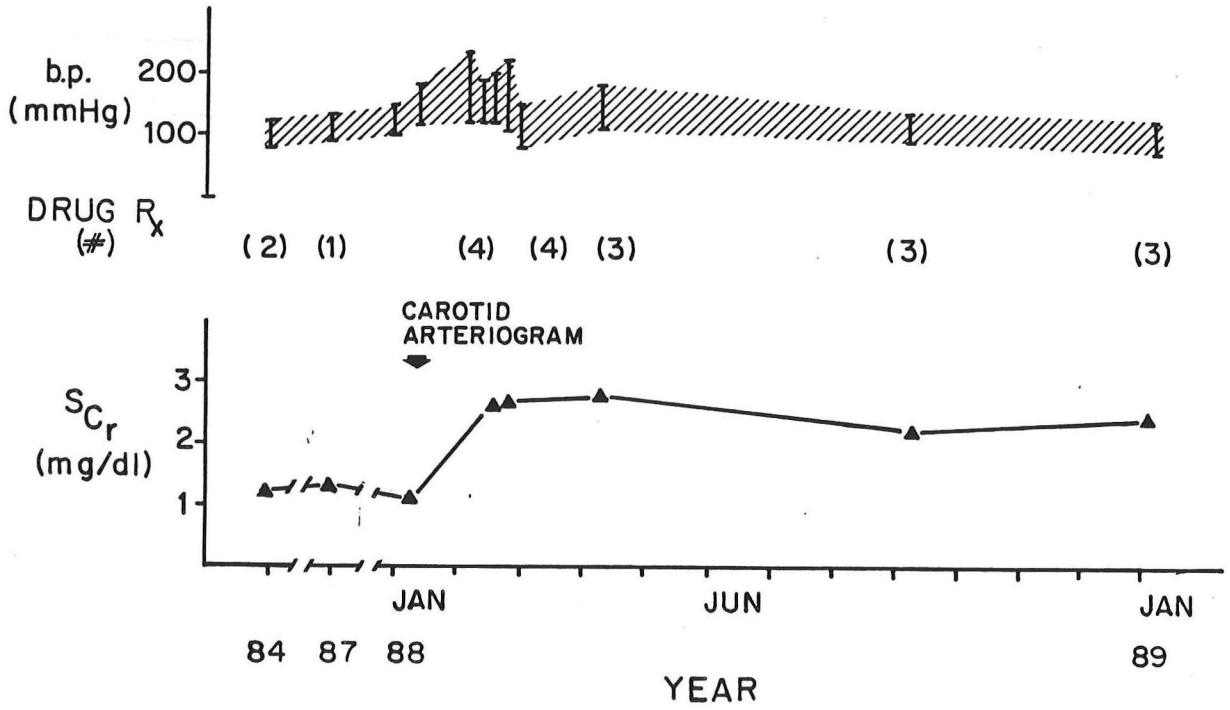


Figure 18

Acute and chronic renal failure are two important disorders resulting from cholesterol embolization. However, the occurrence

of these disorders may be overshadowed by other more devastating systemic consequences or the disorder may be so subtle that it goes undetected for weeks or months. Cholesterol embolization may take one of two forms: 1) detachment of atheromatous plaques from the intimal surface of large vessels which travel distally occluding small arteries or larger arterioles and 2) the release of cholesterol crystals, or microemboli, from the surface of existing ulcerated plaques which travel distally and occlude smaller arterioles. This latter disorder has been called multiple cholesterol embolization syndrome, or MCES (156). The presentation and clinical findings of MCES can mimic 1) polyarteritis nodosa, 2) allergic vasculitis, 3) subacute bacterial endocarditis, and 4) left atrial myxoma prompting Darsee (157) to describe this disease as "the great masquerader". Spontaneous embolization from aortic atherosclerotic plaques causing renal failure is amply documented, but the angiography-induced form of multiple cholesterol emboli syndrome causing acute renal failure is less well described and appreciated. There are indications that the syndrome is not rare but rather many cases may be subclinical in their manifestations.

While the problem of plaque type cholesterol emboli which occlude larger vessels is not rare, the occurrence of micro cholesterol emboli is sometimes more subtle and may go undetected. When it occurs after angiography it generally takes one of two forms. In what has been described as the "catastrophic" or acute form (Table 18), the patient develops symptoms and signs of vessel occlusion during the arteriography procedure (e.g. pain in the legs or feet, abdominal and back pain, numbness, paralysis, agitation,

Table 18

Multiple Cholesterol Emboli Syndrome

Acute or "catastrophic" form

a. agitation, sweating
b. pain in legs or feet
c. abdominal and back pain
d. numbness or paralysis of extremities
e. skin discoloration (livedo reticularis and "purple toes")
f. acute hypertension
g. acute renal failure
h. hypotension
i. death

skin or extremity discoloration). The prognosis for these patients is very poor, as most become hypotensive, oliguric, and die with multiple organ infarctions. In the more chronic, or "non-catastrophic" form (Table 19), the symptoms and signs are less prominent or absent, but the patients frequently develop worsening

Table 19

Multiple Cholesterol Emboli Syndrome

Chronic or "non-catastrophic" form

a. malignant or episodic hypertension
b. post angiography or post operative chronic renal failure
c. acute pancreatitis
d. myopathy
e. peritonitis, bowel ischemia (melena, hematochezia)
f. livedo reticularis
g. gangrene of extremity

hypertension and progression of renal disease. The development of postoperative chronic renal failure or end stage kidney disease requiring dialysis following aortic aneurysm surgery should make the clinician very suspicious of the presence of MCES (158-160). Aortic aneurysm repair is the most common cause of this form of chronic renal failure (159,160). Supporting this is the observation that cholesterol emboli have been found in 25% of patients who undergo this type of surgery (161). Skin changes also may be present. Changes may require 1-4 weeks to develop and it is assumed that subclinical embolization is occurring during this time. Also, there is a variety of clinical conditions that multiple cholesterol emboli syndrome may induce (e.g. acute pancreatitis, malignant hypertension, acute myopathy), that may not be easily traced to cholesterol emboli (162).

Because it may be subclinical, the true incidence of MCES following angiography is difficult to determine. However, a retrospective autopsy study of 71 patients who underwent cardiac catheterization (51) or aortography (20) within 6 months of death by Ramirez et al (163) suggests that the incidence is high. Table 20 shows that the incidence of cholesterol emboli in autopsy

Table 20

Patient Group	No.	No. with emboli	Incidence %
1. Aortogram	20	6	30
2. Cardiac cath with coronary angio	51	13	25.5
3. Controls	70	3	4.3

Ref. 163

material was 25-30% in the patients undergoing angiography compared to 4.3% in a group of matched control patients who had not undergone angiography within 6 months of death. Table 21 describes

the location of the emboli in the three groups and, as might be expected, cardiac catheterization was associated primarily with cholesterol emboli in the myocardium, while aortography caused

Table 21

Localization of cholesterol emboli

Organs involved	Controls	Aortogram	Cardiac cath
Kidney	3	5	1
Spleen	1	4	1
Stomach	-	1	1
Pancreas	-	1	1
Myocardium	-	-	10

Ref. 163

emboli primarily in the kidneys and spleen. None of the patients had vascular surgery after the angiography. As a clinical footnote, 2.8% of patients who had an angiogram had an episode of acute renal failure, while none occurred in the control patients.

The typical patient at risk to develop MCES is a 60 year old male with extensive atherosclerosis of the aorta and clinical evidence of vascular disease in the carotid and femoral arteries (Table 22). The patient may have experienced amaurosis fugax (transient monocular blindness), a transient ischemic episode, a cerebrovascular accident, or intermittent claudication. The patient is likely to have been hypertensive for many years and may have renovascular hypertension. Coronary artery disease is common

Table 22

MCES-Patient Profile

1. 60 year old male
2. Extensive atherosclerosis, esp. aorta
3. Large vessel bruits
4. Amaurosis fugax (transient monocular blindness)
5. Transient ischemic episodes
6. Cerebrovascular accident
7. Intermittent claudication
8. Coronary artery disease
9. Longstanding hypertension
10. Renovascular hypertension
11. Retinal artery cholesterol emboli

in such a patient. Physical exam will often demonstrate bruits over the abdomen and large vessels. Funduscopic exam occasionally reveals bright orange plaques at the bifurcation of retinal arterioles, which are composed of cholesterol crystals, and carry the eponym, Hollenhorst plaques.

Making the diagnosis of MCES when the acute or "catastrophic" form develops is not difficult. Within minutes of the angiogram, malignant hypertension or sometimes hypotension, pallor, sweating, and acute leg pain develop. The skin of the trunk and lower extremities develops a blotchy blue discoloration. When emboli lodge in the digital arteries of the feet, painful purple discoloration of the toes may occur. When purple toes occur apparently in a spontaneous manner, palpation of a pulsatile abdominal mass will frequently point the clinician in the direction of multiple cholesterol emboli. Motor strength of the lower extremities may decrease. Signs suggestive of peritonitis or bowel ischemia often develop (e.g. guarding of the abdomen, loss of bowel sounds, melena, hematochezia). Later, oliguria or anuria develops. Disseminated intravascular coagulation (DIC) may be a terminal event. In the subacute or "non-catastrophic" form, as I believe the patient had in the case report read earlier, a worsening of hypertensive control may be the initial manifestation. The process is probably mediated by renin (164). A rise in the serum creatinine indicates involvement of the kidneys.

Laboratory studies are sometimes helpful in supporting the diagnosis (Table 23). Leukocytosis, eosinophilia, elevated sedimentation rate, mild proteinuria, decreased platelets, and decreased complement have all been described. Of these,

Table 23

MCES-Laboratory findings

1. Leukocytosis
2. Eosinophilia
3. Elevated sedimentation rate
4. Decreased platelets
5. Decreased complement

eosinophilia is the most commonly noted and the reason that polyarteritis is so often considered in the differential diagnosis.

The pathologic findings at autopsy invariably include widespread and severe atherosclerotic changes of the aorta, carotid, iliac, and femoral vessels. Cholesterol microemboli are found typically in the kidney, spleen, stomach, small bowel, pancreas, muscle, and skin (165). The cholesterol emboli are easily detected in the specimens as biconcave, needle-shaped, clefts remaining after dissociation of crystals during routine histologic preparation (Figure 19). At a later stage, foreign-body giant cells appear and still later concentric fibrosis. In the kidney, the cholesterol emboli typically lodge in the arcuate and interlobar arteries and may occasionally be found in glomerular tufts. A necrotizing glomerulonephritis with exuberant extracapillary proliferation was described in one patient

with spontaneous atheroembolic renal disease (166). Multiple occlusions of small arteries in the kidney lead to patchy atrophy of the parenchyma in wedge-shaped zones of infarction. Atheroembolic renal disease should be a prime suspect when wedge-shaped scars and infarcts accompany severe atherosclerotic disease of the aorta, realizing, however, that these changes are not specific for this disorder.

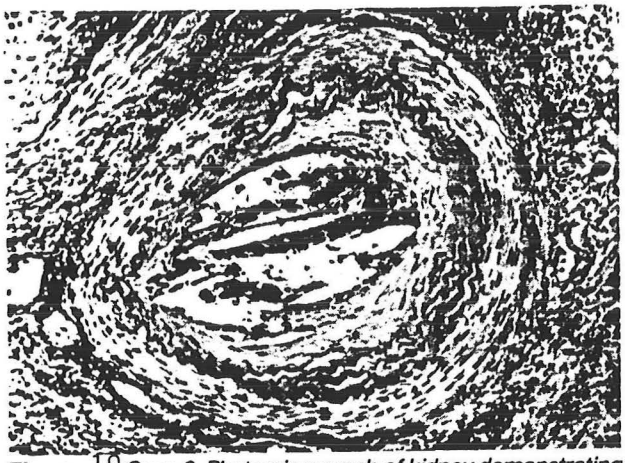


Figure 19 Case 2. Photomicrograph of kidney demonstrating an interlobular artery with the characteristic biconvex, needle-shaped clefts of cholesterol embolization. Hematoxylin and eosin stain; original magnification × 100, reduced by 50 percent. ref 162

Angiography and aortic surgery re the two most important causes of MCES and involve direct dislodgement of embolic from the involved vessels. The case for anticoagulants promoting microemboli is largely circumstantial, but they have been part of the history in a sufficient number of cases to question the use of these drugs in patients with severe atherosclerotic disease (162,163,167-169). Why anticoagulants seem to cause MCES is not known, but prevention of thrombus organization over ulcerated aortic lesions has been suggested (169). Bruns et al (167) described a 55 year old male who spontaneously developed decreased mental acuity, nausea, vomiting, calf pain, and livedo reticularis on the trunk and extremities over a one week period (Figure 20). The patient had been on warfarin for thrombophlebitis. To determine the cause of his deteriorating renal function, a renal biopsy was performed and it showed characteristic findings of cholesterol emboli. The warfarin was discontinued prior to the biopsy and in the week after the biopsy the skin and gastrointestinal signs and symptoms resolved.

ref 167

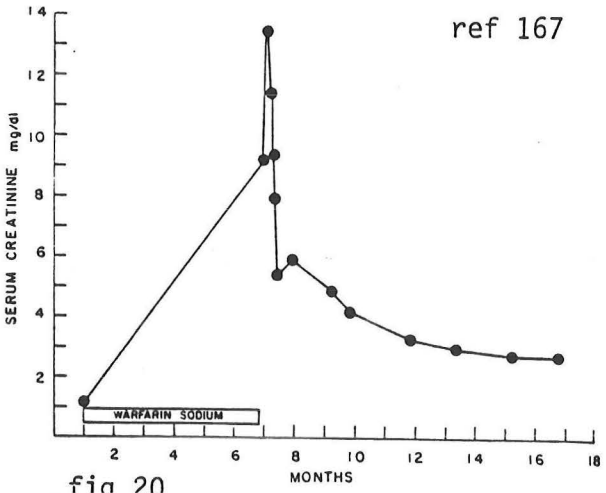


fig 20

Sequential serum creatinine determinations in the patient showing improvement following discontinuation of anticoagulants. Each point represents a single determination.

Meyrier et al (167) reviewed their experience with 32 patients with renal failure and widespread atheroma and noted that 30 of 32 had some degree of renal artery stenosis and 10 of these 30 had cholesterol crystal emboli when the kidney was examined histologically. In two additional patients, renal failure could only be attributed to cholesterol emboli. They have suggested that term "atheromatous renal disease" to encompass those patients with renal impairment due to gross atheromatous involvement of the renal arteries as well as including those

patients with microembolic renal disease. In the 10 patients with multiple cholesterol embolization of the kidneys, it was attributed to renal angiography in 6, anticoagulant overdosage in 3, and renal artery surgery in one. The diagnosis was suggested in 6 by typical skin lesions (purple toes or livedo reticularis).

These authors have suggested that it may be too simplistic to attribute progressive renal disease in hypertensive patients with atherosclerosis simply to progressive nephrosclerosis. Rather, atheromatous renal disease, large vessel and microembolic, may be involved in many of these.

The differential diagnosis of multiple cholesterol emboli syndrome induced renal disease covers a wide spectrum (Table 24). When it occurs following angiography, the most important diagnosis

Table 24

Differential Diagnosis

1. Contrast induced acute renal failure
2. Polyarteritis nodosa
3. Allergic vasculitis
4. Left atrial myxoma
5. Subacute bacterial endocarditis

to exclude is that of contrast-induced renal disease. Contrast induced ARF is not associated with skin or extremity changes, nor is fluctuating or malignant hypertension a major feature. Also, the renal failure has a shorter course, with recovery within 7-10 days being the rule in most patients who previously had normal or near-normal renal function. The hypertension, skin changes, multiple organ involvement, and eosinophilia of MCES can mimic polyarteritis nodosa. Similarly, allergic vasculitis of the Churg Strauss variety was diagnosed in a case that later proved to be MCES (170). Particles of a left atrial myxoma may dislodge into the systemic circulation causing skin and extremity changes that mimic cholesterol emboli. Vegetations from infected heart valves in patients with subacute bacterial endocarditis may embolize and cause lesions similar to MCES. Physical examination and echocardiographic findings should give the right diagnosis of these latter two disorders.

The prognosis of MCES was formerly thought to be uniformly bad. In recent years, more cases have been known to survive, particularly with the help of dialysis therapy. McGowan et al (171) demonstrated that prolonged support with hemodialysis therapy may allow some of these patients to regain a satisfactory level of renal function (Figure 21). This apparent improved ability to cope with this disease probably reflects better detection. When the acute or "catastrophic" form occurs, the organ damage from infarction is usually so severe and widespread that little can be done to permit survival in these patients. A high degree of suspicion is needed to detect the milder, subclinical and chronic forms of MCES.

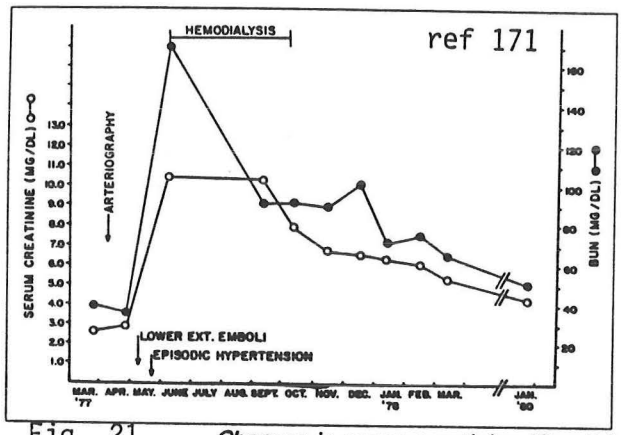


Fig. 21 *Changes in serum creatinine (O—O) and blood urea nitrogen (●—●) over a 34-month period. Arrows indicate inciting arteriography, and episodes of lower extremity emboli and episodic hypertension. Brackets indicate four month period of maintenance hemodialysis.*

The management of the acute form of this disorder is supportive (Table 25). Withdrawal of anticoagulation seems warranted. Plasma expanders, vasodilators, sympathetic blockade,

Table 25

Management of MCES

1. Withdraw anticoagulation
2. Dialysis therapy
3. Prevention

steroids, and anticoagulants all have been tried without success. Peritoneal dialysis (172) and hemodialysis (156,162,171) may be successfully used in certain patients with the hope of some recovery of renal function, provided that the systemic injury is not too severe.

Physicians have an important role in the prevention of this disorder realizing that some cases of MCES occur spontaneously. Anticoagulants should be used cautiously in patients with atherosclerotic vascular disease. Unfortunately, the patients most at risk from angiographic procedures are also these most likely to benefit from the information gained, if corrective surgery can be successfully carried out. Since angiography from the femoral approach seems to be most frequently associated with this complication, consideration should be given to performing the procedure from another site, e.g. brachial or axillary artery, when severe atherosclerosis of the aorta is present or suspected. When

the femoral approach is used, the softest catheter capable of performing the study should be used. Lastly, very careful handling of an atherosclerotic aorta, iliac, and femoral vessels during vascular surgery theoretically might diminish the release of micro cholesterol emboli from atheromatous plaques. However, reports that coughing, tenesmus, and lifting may dislodge plaques and cause renal failure makes such warnings to the surgical team of dubious merit (173). It seems prudent for the physicians recommending and performing the angiography to inform the patient that, in addition to the risk of contrast related problems, cholesterol emboli may be dislodge and a wide range of adverse effects might occur particularly, but not limited to, hypertension and renal insufficiency, particularly since these problems may not become apparent for months later.

In conclusion, radiologic procedures that employ intravascular contrast material with or without angiography may lead to renal failure. Since disorders related to atherosclerotic vascular disease are a major indication for performing angiography, the occurrence of renal failure after angiography has the potential for being due to both contrast and multiple cholesterol emboli. If chronic renal failure or chronic hemodialysis is the final outcome, the likelihood that MCES induced renal failure is present is very high. The clinical pattern of the renal failure and degree of recovery help determine the component of each.

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