Original article

Contrast nephropathy in lower limb angiography

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Aim: This study examines the occurrence of contrast nephropathy in a series of 302 consecutive lower limb angiogram and angioplasty procedures.

Methods: Serum creatinine measurements, 1 and 3 days after the procedures, were used to identify cases of contrast nephropathy, defined as a 25% increase above initial creatinine. These cases were reviewed retrospectively. A total of 267 patients had 224 diagnostic, and 78 interventional lower limb angiographic procedures. Of these, 46% had pre-existing renal impairment (creatinine >118 $\mu\text{mol/l}$), of whom 11% were on dialysis – dialysis patients were excluded from analysis of changes in creatinine. Repeat creatinine measurements were taken after 191 procedures.

Results: Contrast nephropathy occurred after 15 procedures: of whom 9 died, and 6 recovered. Of these patients, 11 were taking potentially nephrotoxic drugs and 9 had renal impairment. Precautions to avoid contrast nephropathy were taken in only 2 cases. Of the 9 deaths, 6 were associated with severe underlying disease processes, but 3 occurred directly as a result of contrast nephropathy. Contrast nephropathy has an incidence of 8% in this series: the incidence in acute limb-threatening ischaemia is double that for other cases. Death from renal failure is relatively rare, with an incidence of 1%. In uncomplicated angiography or angioplasty, where admission is not prolonged by a need for further treatment, the condition has no mortality.

Conclusions: Accepted precautionary measures should be observed, and alternatives to conventional angiography should be considered – particularly where there is pre-existing renal impairment and other co-morbidity.

Key words: Angiography – Contrast media – Kidney failure

Intravascular, iodinated, radiological contrast may induce transient or permanent changes in renal function, evident as elevation of serum creatinine contrast nephropathy. A major epidemiological study of contrast nephropathy in 1826 patients undergoing coronary angiography¹ showed an incidence of 14.5%, but that only 0.77% became dialysis-dependent. The in-hospital mortality for the acute condition was 36%. The incidence of the condition was increased by dehydration, diabetes, pre-existing renal impairment, and use of > 100 ml of intravascular contrast. As a result, precautionary measures have been recommended,² and clinical trials of other preventive measures have been

undertaken.^{3–14} Accepted precautionary measures include avoiding dehydration, stopping nephrotoxic drugs, and minimising contrast volume. In lower limb angiography, however, contrast nephropathy is given little consideration.

This study determines the incidence of contrast nephropathy in lower limb angiography, identifies the circumstances in which it occurs, and examines the use of precautionary measures.

Patients and Methods

Retrospective analysis of computerised records was performed, for all patients undergoing lower limb angio-

graphy or angioplasty in the radiology department of the Royal London Hospital between 1 January 2001 and 31 December 2001. All procedures were performed with non-ionic, iodinated contrast media: Omnipaque 300 (Nycomed), or lower osmolality Visipaque 320 (Nycomed) for patients with established renal failure. Emergency angiography in the operating theatre, endoluminal aneurysm repair, and combined surgical and radiological procedures were not included. Contrast nephropathy was defined as a 25% increase over initial creatinine in the 3 days following the procedure.¹ Patients on dialysis were not included in this analysis. The case-notes of all incidents of contrast nephropathy were examined retrospectively to determine the circumstances in which the problem arose and the outcome.

Results

The study group of 267 patients underwent a total of 302 procedures over 1 year: 224 diagnostic angiograms, 75 angioplasties, and 3 combined angioplasty and stent procedures. A total of 33 procedures were performed on dialysis patients – changes in serum creatinine are not valid in these cases, and they have been excluded from analysis. Of the non-dialysis cases, repeated creatinine measurements were performed following 191 procedures; 78 cases were discharged on the day of the procedure without 1–3 day creatinine measurements.

Contrast nephropathy occurred after 15 (8%) procedures. Table 1 shows the characteristics for cases, comparing those who did not develop contrast nephropathy with those who did. Percentages have been used to allow comparison of proportions; it is accepted that percentages are not ideal for use where small numbers are considered.

Table 2 compares the incidence and mortality of contrast nephropathy for patients: (i) who were discharged within 5 days after uncomplicated angiography or angioplasty; (ii) who stayed for further treatment; and (iii) patients with acute limb-threatening ischaemia.

The risk factors, use of precautionary measures and outcome for patients who developed contrast nephropathy are shown in Table 3. Three patients with contrast nephropathy died as a direct result of renal failure. The first was 96 years of age, and on digoxin for atrial fibrillation, but had good out-door mobility and led an independent life. She presented with acute femoral embolism. The initial creatinine level was significantly raised at 224 $\mu\text{mol/l}$.

Table 1 Comparison of patient characteristics

	No contrast nephropathy	Contrast nephropathy
Age (years)		
Mean:	69	77
Range:	25–93	67–96
Diabetes	17% (30/176)	13% (2/15)
Renal impairment	45% (80/176)	60% (9/15)
Initial mean creatinine ($\mu\text{mol/l}$)	118 (SD 44.65)	148 (SD 76.00)
Number of procedures	176	15
Multiple procedures	10% (17/176)	27% (4/15)

Angiography was performed with non-ionic contrast (Omnipaque 300). The patient underwent successful femoral embolectomy under local anaesthesia. Creatinine measurements continued to rise – on the 5th day, renal physicians considered contrast nephropathy to be the cause: she was managed by stopping the angiotensin converting enzyme inhibitor, and supplementary intravenous fluid. On the 8th day, she died of asystolic cardiac arrest with associated hyperkalaemia.

The second fatality was 72 years of age, not limited by cardiorespiratory symptoms, but severely limited by chronic lower limb ischaemia which had deteriorated to dry ulceration. The initial creatinine level was mildly elevated at 127 $\mu\text{mol/l}$. Angiography was performed with non-ionic low osmolality contrast (Visipaque 320). Following the procedure, she was thought to have poor urine output and was given additional frusemide. She was reviewed by the renal physicians on the 5th day and managed by supplementary intravenous hydration; however, she suffered a cardiac arrest and died 2 days later.

The third case was 95 years of age and limited by chronic lower limb ischaemia, which had deteriorated to dry gangrene of the toes. He was managed medically for diabetes-related chronic renal failure, with an initial creatinine level of 332 $\mu\text{mol/l}$. Angiography was performed with non-ionic low osmolality contrast (Visipaque 320). He underwent above-knee amputation the following day. His renal failure deteriorated immediately after angiography and did not recover. He acquired wheelchair mobility and was discharged home with support. The patient was re-admitted 6 weeks later by the renal physicians with uraemia and fluid overload; he suffered a

Table 2 Comparison of incidence and mortality of contrast nephropathy for different groups

Contrast nephropathy	Incidence	Mortality
Uncomplicated procedure and discharge by 5 days	5/110 (4.5%)	0/5 (0%)
Further intervention required/unfit for discharge	7/129 (5.4%)	6/7 (85%)
Acute limb-threatening ischaemia	3/31 (9.7%)	3/3 (100%)

Table 3 Cases of contrast nephropathy – risk factors, precautions, and outcome

Indication for procedure	Co-morbidity	Age (yr)	Diabetes	Initial creatinine ($\mu\text{mol/l}$)	Nephrotoxic drugs	Drug withheld	Intravenous hydration	Outcome
Rest pain	COPD, CCF	92		111	Furosemide, aspirin	No	No	Died – untreated gangrene
Acute embolic ischaemia	AF, peritonitis	70		57	Aspirin	No	Yes	Died – untreated gangrene
Acute embolic ischaemia	AF	96		224	ACE	No	No	Died – ARF
Claudication		77		103	ACE	No	No	Recovered
Rest pain		77		115	ACE	No	No	Died – haemorrhage during thrombolysis
Rest pain		75		76	Aspirin	No	No	Died – Mesenteric infarction
Claudication		84		121	Furosemide	No	No	Recovered
Claudication		73		156			No	Recovered
Rest pain, ulceration	COPD, CCF	86		144	Furosemide, ACE, aspirin	No	No	Died – MI
Ulceration	COPD	72		127	Furosemide	No	No	Died – ARF
Claudication		67		104			No	Recovered
Gangrene	AF	67		151	ACE	No	No	Died – MI
Gangrene		95	Yes	332			No	Died – CRF
Gangrene	AF	77	Yes	287	Aspirin	No	Yes	Recovered
Claudication		73		120			No	Recovered

COPD, chronic obstructive pulmonary disease; CCF, congestive cardiac failure; AF, atrial fibrillation; ACE, angiotensin converting enzyme inhibitor; ARF, acute renal failure; CRF, chronic renal failure; MI, myocardial infarction.

cardiac arrest and died.

Discussion

The incidence of contrast nephropathy in this series (8%) is lower than that observed in coronary angiography (14%). This is surprising, as many of our patients should be particularly at-risk because lower-limb angiography usually requires contrast volumes greater than 100 ml and a large proportion of patients have diabetes or pre-existing renal impairment. The incidence depends upon what is regarded as a significant change in serum creatinine concentration. We have used the most commonly used definition – a 25% increase above the initial creatinine level.¹ The series of procedures was prospectively recorded and is, therefore, complete; however, the study was retrospective and, as a result, patients discharged the day of the procedure lacked 1–3 day creatinine measurements. These were likely to be fit patients who had limited procedures, although 17 of these cases had mild pre-existing renal impairment (serum

creatinine concentration $>118 \mu\text{mol/l}$). The computerised hospital admission records for these 78 patients have been examined: none have since been referred to or re-admitted by renal physicians. The creatinine changes observed in this study may, therefore, be more representative of unhealthy patients.

The characteristics which may be associated with increased susceptibility to contrast nephropathy are compared in Table 1. The mean age is greater for the contrast nephropathy group (77 years) than for the no-contrast nephropathy group (69 years). The age range of the no-contrast nephropathy group is skewed by 3 relatively young patients with vascular traumas and it must be noted that some quite elderly patients had angiography without problems. Diabetes is considered to double the likelihood of contrast nephropathy,¹ but in this series this was not the case – the incidence of diabetes was slightly less in the no-contrast nephropathy group (13%). In our series, the mean creatinine concentration for those who developed contrast nephropathy ($148 \mu\text{mol/l}$) was higher than that for those who did not ($118 \mu\text{mol/l}$), and a

greater proportion of patients who developed contrast nephropathy had pre-existing renal impairment (60%) than those who did not (45%). A greater proportion of patients who developed contrast nephropathy had multiple episodes of contrast exposure (27%), than those who did not (10%).

The incidence of contrast nephropathy shown in Table 2 is slightly greater for patients who stay for intervention, and there is a no contrast nephropathy-associated mortality for patients who have uncomplicated angiography or angioplasty. Acute limb-threatening ischaemia doubles the incidence of contrast nephropathy and, for this group, there is 100% mortality.

Contrast-induced changes in serum creatinine are only of importance if they result in morbidity and mortality. In this series, 6 of the 15 cases who developed contrast nephropathy died within 30 days of the procedure, and a further 3 died within 6 months giving an overall mortality of 60%. The important question is whether these deaths were related to the contrast-induced injury. Table 3 shows that 2 patients probably died because of the severity of their vascular disease, 1 died from mesenteric infarction, 1 died from complications of thrombolysis, and 2 died from myocardial infarction. The three cases who died from renal failure suffered cardiac arrest associated with electrolyte disturbance. Two of these cases had undergone successful treatment of the underlying vascular problem (limb salvage by embolectomy, or amputation of a gangrenous foot), but the other was awaiting a management decision. Two died within 30 days during the initial hospital admission and one was re-admitted after out-patient management by the renal physicians. No patients had dialysis. The 6 patients who recovered completely, recovered quickly – serum creatinine concentrations dropped below the 25% increase level within 5 days.

Cases where significant changes in serum creatinine occur after lower limb angiography fall into three categories: (i) short-term changes of no significance (6/15); (ii) changes associated with significant underlying pathology leading to death (6/15); and (iii) changes resulting from contrast-injury leading to renal failure and death (3/15). All of this last group had pre-existing renal impairment and two were of advanced age.

Accepted measures to avoid contrast nephropathy include maintenance of hydration, and stopping potentially nephrotoxic drugs.² Controlled trials of other preventative measures include: forced diuresis;³ dopamine;⁴⁻⁷ *n*-acetyl cysteine;⁸ theophylline;⁹ atrial natriuretic peptide;¹⁰ and the use of dialysis to remove contrast media.¹¹⁻¹⁴ Results for *n*-acetyl cysteine are encouraging, but the incidence of contrast nephropathy in the control group of this study is unusually high (9/42) in spite of small contrast doses (mean, 90 ml). Accepted precautionary measures were not used in 13 of our

cases where contrast nephropathy developed. Of this group, 11 patients were on potentially nephrotoxic drugs – none were stopped prior to the procedures. Only 2 patients received intravenous hydration. It is also worrying that one of our patients received frusemide following angiography to treat oliguria.

Alternatives to angiography using standard iodinated contrast media, should be considered for patients with renal impairment, advanced age and other co-morbidity. Carbon dioxide can be used as intravascular contrast. It is not nephrotoxic, and is rapidly excreted by the lungs; although it is contra-indicated in the proximal aorta, subclavian and carotid circulation, as carotid studies in rats resulted in cerebral infarction.¹⁵ Resolution is less than with iodinated contrast, but digital subtraction can sufficiently compensate, to allow adequate imaging of the aorta and lower limb arteries.¹⁶ Small series also suggest that gadolinium has potential as a safe, alternative intravascular contrast medium.^{17,18} MRI angiography and duplex ultrasound are well-established, safe alternatives to invasive contrast angiography.

Finally, it is important to consider that sensible management decisions can sometimes be made without need for vascular imaging at all. Patients with severe ischaemia who have significant co-morbidity may benefit from amputation without attempted limb salvage and, in some cases, palliative or terminal care.

Conclusions

Contrast-induced changes in serum creatinine concentrations occur in 8% of cases undergoing lower-limb angiography. Only 20% of these lead to death from renal failure: this occurs in patients with acute limb threatening ischaemia who have double the incidence of contrast nephropathy and in those who require further treatment. Of the remainder, 40% are transient changes of little significance; and 40% occur in conjunction with a severe underlying disease process, which then leads to death. Accepted precautionary measures are not being adhered to.

Those managing patients undergoing lower limb angiography should be aware that, although contrast nephropathy is rare, it can lead to persisting renal failure and death. Care must be taken to monitor serum creatinine concentrations, stop nephrotoxic drugs, and maintain hydration. Alternatives to angiography with iodinated contrast should be considered for patients with pre-existing renal impairment, advanced age, and other co-morbidity.

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