
Renal protection during intervention

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Abstract

Early renal failure following endovascular intervention for renovascular disease is well recognised. It is less likely to be due to technical complications as to cholesterol embolisation or contrast nephrotoxicity. How important are these and do we need to protect the kidney against their effects during intervention?

Keywords: Endovascular intervention; renal failure; cholesterol embolisation; contrast nephrotoxicity.

Introduction

Protection is defined as 'the act of defending from trouble, harm or attack'^[1]. There are many things that can go wrong during any endovascular intervention and for the most part these can be kept to a minimum by training, experience and clinical judgment. However, despite these safeguards, there are some complications in renal intervention that occur due to the pathophysiology of the disease, or the chemical agents used to define it. These are usually due to atherosclerotic embolisation and renal infarction, or contrast nephrotoxicity, and can cause either insignificant temporary or devastating permanent renal failure. In the last 2 years, various mechanical devices^[2] and pharmacological agents^[3] have been developed that might protect the kidney from such insults during endovascular interventions. Do they work and are they necessary in all cases?

The two most common causes of renovascular disease are atherosclerosis and fibromuscular dysplasia. Others such as neurofibromatosis and aortic dissection are more rare, though Takayasu's disease is very common in the Far East and South America. Endovascular treatment of such symptomatic diseases in the renal arteries is now widely accepted as being relatively safe and efficacious in the right clinical setting. However, renal failure following intervention, due to atheroembolism or contrast toxicity, is only described in atherosclerotic renovascular disease, usually (though not exclusively) where there is a degree of pre-existing renal failure. It would seem therefore that

protection is unnecessary in all cases, but that we should examine its potential in the atherosclerotic patient.

The incidence of renal insufficiency post-endovascular renal intervention

An analysis of the literature from 24 published series in the 1990s citing 1187 patients who had undergone percutaneous transluminal renal angioplasty (PTRA), with or without stenting, for atheromatous renovascular disease, reveals a 1% incidence of permanent renal insufficiency and a 3.3% incidence of temporary renal insufficiency^[4]. Segmental infarction occurs in 1.3% but is significant in less than 1%.

Two more recent papers from Henry *et al.*^[5,6] described follow-up in 269 patients who had renal stent implantation for mainly ostial atherosclerotic renovascular disease. Most of these patients had undergone suboptimal PTRA suggesting that the degree of manipulation was maximal and that not insignificant amounts of contrast were used. Though the papers do describe a small number of mechanical complications, neither paper describes any incidence of clinically significant atheroembolism or contrast nephrotoxicity. It is not surprising therefore that the same group later found no evidence of renal insufficiency after using an atheroembolic renal protection device, in a different cohort of patients undergoing renal stenting for ostial atheromatous renal artery stenosis (RAS)^[2]. What is surprising is that they should recommend the routine use of a protection device in all renal interventions.

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Cholesterol embolisation or contrast nephrotoxicity?

None of the above papers mention the role of contrast as a nephrotoxic agent or the use of pharmacological protection. Indeed when discussing post-interventional renal failure, few authors consider both atheroembolisation and contrast nephrotoxicity together though there is literature evidence that the latter is the more important factor prognostically^[7]. Unless the patient has the rare clinical signs of livido reticularis with a raised ESR, C reactive protein (CRP) and an eosinophilia, it is impossible to know in the early phase whether a rise in creatinine is due to cholesterol or contrast. The more insidious late rise in creatinine occasionally seen is often blamed on embolisation, but can equally be due to poor patient selection for intervention or progressive atherosclerotic disease. Even renal biopsies are unhelpful at this stage as cholesterol clefts can be seen in many of these patients where no intervention has taken place^[8].

Atheroembolisation and the need for protection

Thurlbeck and Castleman^[8] showed that in post mortem analysis of aortic aneurysm repair followed by death there was an incidence of renal atheroembolic disease of greater than 70%. They also showed however that there is a greater than 20% incidence of atheroembolic disease in individuals with no intervention but severe aortic atherosclerotic disease. Flory^[9] demonstrated that the emboli are cholesterol crystals.

What is the data available on embolisation during endovascular interventions?

Muscle biopsies in patients undergoing angiography alone have shown subclinical cholesterol embolisation in 25% of patients^[10]. This, in addition to the fact that cholesterol can be found in renal biopsies where there is no intervention, would suggest that ostial plaque is inherently unstable. Rapp *et al.*^[11] using an *ex vivo* preparation of carotid arteries with intervention and analysis of effluent showed that emboli were produced at all stages of an intervention from the passing of an initial fine guide wire, through percutaneous transluminal angioplasty (PTA) to stent insertion.

If embolisation is the usual case during intervention, why is it not more often a clinical problem?

Kimura *et al.*^[12] using microspheres to mimic atheroembolic disease suggested that cholesterol crystals occlude arteries between 55 and 900 μm in diameter. In the kidney these would correspond to renal arteries of interlob-

ular and arcuate size down to glomerular capillaries. The outcomes in terms of proteinuria and renal dysfunction were dose dependent. Only with larger doses of microspheres did proteinuria occur and only at the largest dose was there a decline in renal function. With low doses of microspheres there was no proteinuria or renal dysfunction. This effect took 12 weeks to occur. This is in keeping with the insidiously progressive form of atheroembolic disease rather than the acute catastrophic form described following renal intervention. So the clinical effect of cholesterol embolisation appears to be dose dependent.

What is the cholesterol load to the kidney during intervention?

This is difficult to determine. There has been Doppler analysis of cerebral blood flow during carotid intervention^[13]. Despite claims to the contrary these signals could represent cholesterol, air or, most likely, both. There are no data on renal artery Doppler recognition of emboli and intervention. However Al-Hamali *et al.* recorded Doppler signals over the femoral arteries after iliac angioplasty^[14]. Their control group consisted of patients undergoing renal angioplasty. Although the signal was low compared to iliac angioplasty there were embolic events recorded for 2 h after renal angioplasty in the femoral arteries. Does this suggest that the embolic load during PTRAs would be even greater to the target organ or could it be that sheer stress due to flow in an artery at right angles to the aorta is actually partly renoprotective?

Can we prevent embolisation during intervention?

There are three types of atheroembolic protective device from a number of manufacturers. One developed for carotid angioplasty and stent placement involves reversal of blood flow through the carotid during the angioplasty procedure and is not applicable to the renal artery. The second type of device is the occlusion balloon and is the type used in the study by Henry *et al.*^[2]. It has a crossing profile of 2.7 Fr, which is just under 1 mm. This would be about the size of the channel in a critically stenosed 6 mm diameter renal artery. One could easily see how the manipulation of such a device across a tight stenosis could dislodge unstable plaque as previously demonstrated^[11]. In addition its deployment position might be difficult with early branch vessel division. It also relies on aspiration of effluent after stent deployment. There is no evidence that aspiration can be completely performed. The third type of device is a filter that is deployed distal to the angioplasty site to catch some of the fragments that may be dislodged. The crossing profile of these devices is from 3.1 to 3.9 Fr. They are therefore even more likely to dislodge plaque during manipulation. The pore sizes of the available filters vary from 80 to 150 μm . Kimura's work^[10] has demonstrated that

smaller cholesterol crystals can still obstruct glomerular capillaries. In addition, the deployment problems cited for the balloon occlusion device also apply to these filters.

What evidence is there that filters might be effective during renal intervention?

Baim *et al.*^[15] randomised 800 patients to stent placement with or without a balloon protective device during coronary intervention. There was a significant reduction in death, myocardial infarction and emergency bypass, from 16.5 to 9.6%. However the capacity of the myocardium to withstand emboli is probably very different from the nephrons. The only paper on the use of protection devices in the renal arteries is the previously cited preliminary report by Henry *et al.*^[2]. Here a balloon occlusion device was also used. The patients had excellent initial renal function and were undergoing intervention for hypertension control. The authors noticed no change in renal function on follow-up but found debris with all the patients of a size that would fit the vessel size affected in the Flory paper^[9].

It is clear that atheroemboli are the rule in any intervention in atherosclerotic disease. However it is also clear that important clinical sequelae are uncommon. Renal angioplasty and stent placement will release atheroemboli to the renal circulation but this is mainly in low dose and the effect is not overwhelming as angioplasty/stent placement are associated with an improvement in renal function. It is unlikely that any protection device will preclude all cholesterol embolisation: experimental data shows that even the guide wire will produce this. However it is also possible that the heterogeneous response of kidneys to angioplasty with atherosclerotic disease compared to the beneficial response to angioplasty in fibromuscular dysplasia may depend on the dose of cholesterol crystals released by the procedure. At present neither of the two randomised trials underway in Europe (STAR: Stent Placement and Blood Pressure and Lipid-lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery, and ASTRAL: Angioplasty and Stent for Renal Artery Lesions—<http://www.astral.bham.ac.uk>) have addressed the issue of protection devices. It may be possible that smaller trials, which include those most at risk with single kidney function measurements, can be performed to address this issue. Until that is done the costs and extra manipulations involved with renal protection devices cannot be justified.

Contrast nephrotoxicity and the need for protection

Contrast-associated nephropathy is a potentially serious sequelae of contrast media that manifests as symptoms

ranging from acute, irreversible renal failure to minor changes in tubular function. Indeed in diabetics with pre-existing renal failure who have been dehydrated prior to pyelography with ionic contrast media, the incidence of significant creatinine rise is greater than 90%^[16]. However the use of non-ionic media and pre-procedural hydration reduces this to between 0 and 3%^[17]. Nevertheless the incidence of acute renal failure due to contrast agents surpasses that due to aminoglycoside antibiotics^[18]. Those at highest risk remain those with diabetes and pre-existing renal failure where the incidence of contrast nephropathy remains high at 10–35% despite non-ionic media and hydration^[3]. Where there are no risk factors nephrotoxicity is not a problem^[19] though if patients are studied carefully a ‘creatinine bump’, consisting of a transient increase in serum creatinine of 0.5 $\mu\text{g}/\text{dl}$ over baseline at 48 h, can be seen^[7].

The exact mechanism is poorly understood but it is believed to be vasoconstrictive, affecting the outer medulla where most of the metabolic effort involving ion exchange occurs. This causes ischaemia to the tubular cells in the ascending limb and cellular damage ensues. Like ischaemia elsewhere this is mediated by free radicals. Many drugs have been tested and found to have no valuable protective effect. These include frusamide, natriuretic peptide, theophyllines, calcium channel blockers, endothelin and prostaglandin E1. N-acetylcysteine, a free radical scavenger, has been shown in two studies to be effective at preventing renal deterioration due to contrast toxicity^[3,20]. However three other studies have failed to show any benefit^[21–23]. More recently feneldopam mesylate, a dopamine type 1 receptor agonist, has been shown to be a potent vasodilator of the medullary tubular arteries, to completely eliminate the contrast-induced ‘creatinine bump’ in all patients and to reduce significant increases to less than 4% in the high-risk population^[24]. However it can cause hypotension.

Recent trials of iso-osmolar contrast agents have suggested that rises in serum creatinine are insignificant when compared to other low-osmolar contrast agents in the high-risk population. This is important and suggests that both during intervention and diagnostic investigations, iso-osmolar agents should be used. The use of CO₂ angiography in these patients, which is non-nephrotoxic but expensive, difficult to use and not tolerated by many, is unnecessary if these iodine-based contrast agents are used^[25,26].

Conclusion

Clinically significant renal failure due to atheroembolism and/or contrast toxicity during endovascular renal interventions has an incidence of 1–3%. The group at highest risk is diabetics with pre-existing renal failure. There is no evidence at the present time for the use of balloon occlusion or filtration protection devices during renal

intervention. The evidence for the use of pharmacological protection is conflicting. There is evidence from two well designed randomised controlled trial (RCTs) that iso-osmolar contrast does not induce contrast nephropathy and the importance of adequate hydration is very clear.

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