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EDITORIAL

How to Reduce the Risk of Acute Kidney Injury in Abdominal Aortic Aneurysm Surgery: The Quest of the Grail

While the results of prophylactic abdominal aortic aneurysm (AAA) repair have steadily improved over recent decades, the incidence of acute kidney injury (AKI) remains high.[1] AKI can be associated with increased post-operative mortality, need for renal replacement therapy (RRT), longer hospital stay, and higher healthcare costs with even a residual risk of death at least one year after surgery.

The incidence of AKI after AAA repair can vary according to the type and complexity of surgical treatment, the patient's risk factors, and the definition of AKI used.[2] Since 2012, the universally accepted criteria recommended for AKI identification and severity classification are those defined by the Kidney Disease Improving Global Outcomes guidelines, including both serum creatinine (sCr) level and urine output (UO).[3] Three stages have been defined for AKI severity evaluation, the third one usually linked to RRT.

Open AAA repair (OAR) continues to be used in patients unsuitable for endovascular aneurysm repair (EVAR), as well as in countries where healthcare resources are limited. While infrarenal aortic cross clamping is preferred, suprarenal or supracoeliac clamping may be necessary if the aneurysm extends above the renal arteries, increasing rates of AKI and peri-operative morbidity. Similarly, in the case of a hostile neck, the suprarenal portion of the aorta can be used for sealing fenestrated (fEVAR), branched (bEVAR), or chimney grafts.[2] The complexity of surgery is associated with a potential risk of longer procedure time and the use of more contrast, well known factors for AKI.[1]

Careful management of patients at high AKI risk includes optimising the volume status and haemodynamics (maintenance of adequate blood pressure) and avoiding nephrotoxic agents and hydroxy starch colloid solutions. This can reduce (but not suppress) the development and morbidity of peri-operative AKI.

In this issue of *EJVES*, Saratzis *et al.*[4] report an AKI incidence of 28% after AAA repair in a multicentre UK prospective cohort including 300 patients (91% males, mean age 71 years), some submitted to complex surgery with f/b EVAR and OAR. While 24% developed stage 1 AKI, renal decline (estimated by a drop of estimated glomerular filtration rate [eGFR] $>$ 20%) occurred in $>$25% (37% after fEVAR) at 30 days and reached 30% at one year, despite following the aforementioned recommendations.

CAN THE INCIDENCE OF ACUTE KIDNEY INJURY AFTER AAA REPAIR BE DECREASED?

Therapeutic choices in AKI are still confined to supportive care and preventive strategies. For the prevention of AKI, it is first important to identify the patient related factors, such as older age and pre-existing CKD, procedure related factors, such as the complexity of surgery, and procedure related complications, such as sepsis.

sCr must be measured immediately prior to surgery in all patients, and by using sCr based eGFR equations kidney function can be determined in patients with a steady state pre-operatively so as to ascertain AKI post-operatively. The patients must then be re-assessed within the first 12 post-operative hours incorporating intra-operative and post-operative variables, such as UO. A possible error here could be an overestimation of baseline kidney function, erroneously reassuring the physician owing to inaccuracy of sCr as a marker of eGFR in some populations (the very elderly, those with low muscle mass, those overhydrated by haemodilution). In patients at high risk of AKI, some authors recommend measuring tubular damage biomarkers such as urinary TIMP2●IGFBP7 (a combination of tissue inhibitor of metalloproteinase-2 and insulin like growth factor binding protein-7, two cell cycle arrest biomarkers). It is speculated that such early biomarkers potentially may provide earlier diagnosis and also prognosis information independent of the conventional sCr and UO markers of AKI.[5] However, currently, the benefit and cost effectiveness of this strategy still need validation.

Prevention also needs to understand the mechanisms of AKI that are multifactorial

According to the recent consensus for cardiac and vascular surgery associated AKI prevention,[3] in the pre-operative stage, withholding renin angiotensin blockers and limiting large use of intravenous contrast agents can reduce the incidence of AKI. In the peri-operative period, haemodynamic optimisation to maintain renal perfusion is crucial. The quality of EVAR techniques should also be improved, with less irradiation, contrast use, and aortic manipulation with its high risk of athero-emboli and lengthening of procedure time. Aortic clamping above both renal arteries increases the incidence of AKI. Cold renal perfusion has been suggested for pararenal AAA surgery. Embolic protection devices may help to prevent procedure related athero-emboli during endovascular renal intervention. In the post-operative period, maintenance of haemodynamics

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(mean arterial pressure > 65 mmHg), avoidance of nephrotoxic agents, and prevention of sepsis remain crucial.

Some hopes for better prevention of AKI were invested in remote ischaemic preconditioning, but the results have been conflicting in vascular surgery.[6,7] Two other recent methods seemed to be more promising and are the target of active research. The first hope is the use of mesenchymal stem cell (MSC) therapy administered just before high risk surgery with ischaemia reperfusion.[8] These MSCs have immunomodulatory and tissue repairing properties and may represent a novel approach in AKI for renal ischaemia reperfusion. However, in cardiac surgery, the results of the first clinical trial were neutral.[9] Additional work in vascular surgery is needed.

The second hope comes from the nicotinamide adenine dinucleotide (NAD^+) store restoration, which can be associated with less AKI in ischaemic conditions.[10] Indeed, NAD^+ is a universal electron acceptor from glycolysis and the Krebs cycle, and the substrate for non-redox enzymes that consume NAD^+ at the mitochondria. In critically ill patients, there is a huge metabolic stress, which can lead to AKI. In humans, the urine of those who will develop AKI has a higher concentration of quinolinate and an elevated urinary quinolinate/tryptophan ratio due to a decrease in the activity of the enzyme quinolinate phosphoribosyltransferase, which defends NAD^+ and mediates resistance to AKI. During a pilot study performed in 55 people, with once daily administration by mouth or orogastric tube, the day prior, the day of, and the day after on pump cardiac surgery, of a high dose (1–3 g/day) of nicotinamide, a dose related increase in circulating NAD^+ metabolites was observed, with good tolerance of the drug and less AKI development. This is promising but needs to be confirmed in a larger study.[11]

The take home message from the work published by Saratzis *et al.*[4] is that, despite careful measures, the incidence of AKI after AAA repair remains high. This emphasises the need for continuous research to improve the diagnosis, prevention, and treatment of AKI after aortic surgery. In the meantime, we need to continue to follow the advice of the recently published AAA clinical practice guidelines of the European Society for Vascular Surgery: "In patients undergoing abdominal aortic aneurysm repair, assessment of preoperative kidney function by measuring serum creatinine and estimating GFR is recommended, and those with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) should be quickly referred to a renal physician".[12]

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