Eur J Vasc Endovasc Surg (2017) ■, 1–8

Pre-operative Functional Cardiovascular Reserve Is Associated with Acute Kidney Injury after Intervention

A. Saratzis [a,*], J. Shakespeare [b], O. Jones [a], M.J. Bown [b], A. Mahmood [c], C.H.E. Imray [c,d,e,f]

[a] NIHR Leicester Cardiovascular Biomedical Research Unit, University of Leicester, Leicester, UK
[b] Department of Respiratory Physiology and Sleep, University Hospital Coventry and Warwickshire, UK
[c] Department of Vascular Surgery, University Hospital Coventry and Warwickshire, UK
[d] Warwick Medical School, Coventry, UK
[e] Coventry University, Coventry, UK
[f] Royal College of Surgeons, London, UK

WHAT THIS PAPER ADDS

The impact of cardiovascular reserve on acute kidney injury (AKI) after endovascular surgery remains unclear. It is still unsure whether AKI is related mostly to pre-existing occult comorbidities, such as cardiovascular disease, or procedure related parameters. Hence, developing an adequate reno-protective strategy is not an easy task. A population who traditionally have low cardiovascular reserve and are at high risk for AKI was analysed, and it was shown that AKI after endovascular intervention is associated with pre-operative cardiovascular reserve, independent of other risk factors. This offers insight into what drives AKI development after endovascular intervention and where preventative measures should focus.

Background: Acute kidney injury (AKI) is a common complication after endovascular intervention, associated with poor short and long-term outcomes. However, the mechanisms underlying AKI development remain poorly understood. The impact of pre-existing cardiovascular disease and low cardiovascular reserve (CVR) in AKI is unclear; it remains unknown whether AKI is primarily related to pre-existing comorbidity or to procedural parameters. The association between CVR and AKI after EVAR was therefore assessed.

Methods: This is a case control study. From a database of 484 patients, 292 undergoing elective endovascular aneurysm repair (EVAR) of an infrarenal abdominal aortic aneurysm (AAA) in two tertiary centres were included. Of these, 73 patients who had developed AKI after EVAR were case matched, based on pre-operative estimated glomerular filtration rate (eGFR; within 5 mL/min/1.73 m^2) and age, with patients who had not developed AKI. Cardiopulmonary exercise testing (CPET) was used to assess CVR using the anaerobic threshold (AT). Development of AKI was defined using the Kidney Disease Improving Outcomes (KDIGO) guidance. Associations between CVR (based on AT levels) and AKI development were then analysed.

Results: Pre-operative AT levels were significantly different between those who did and did not develop AKI (12.1±2.9 SD vs. 14.8±3.0 mL/min/kg, $p < .001$). In multivariate analysis, a higher level of AT (per 1 mL/min/kg) was associated with a lower odds ratio (OR) of 0.72 (95% CI, 0.63–0.82, $p < .001$), relative to AKI development. A pre-operative AT level of < 11 mL/min/kg was associated with post-operative AKI development in adjusted analysis, with an OR of 7.8 (95% CI, 3.75–16.51, $p < .001$). The area under the curve (receiver operating characteristic) for AT as a predictor of post-operative AKI was 0.81 (standard error, 0.06, 95% CI, 0.69–0.93, $p < .001$).

Conclusions: Poor CVR was strongly associated with the development of AKI. This provides pathophysiological insights into the mechanisms underlying AKI.

Article history: Received 6 September 2016, Accepted 24 January 2017, Available online XXX

Keywords: Acute kidney injury, Acute renal failure, Cardiovascular reserve, Risk factor

INTRODUCTION

Acute kidney injury (AKI) may occur in up to 20% of patients undergoing vascular intervention.[1,2] Over both the short and long-term, development of AKI[3] has been associated with increased morbidity rates, hospital stay, treatment cost, and mortality.[2,4] This is independent of renal function recovery, based on routinely used parameters such as

* Corresponding author. Department of Cardiovascular Sciences & NIHR Cardiovascular Biomedical Research Unit, University of Leicester, Leicester Royal Infirmary, Leicester LE1 5WW, UK.
E-mail address: as875@le.ac.uk (A. Saratzis).

http://dx.doi.org/10.1016/j.ejvs.2017.01.014

Please cite this article in press as: Saratzis A, et al., Pre-operative Functional Cardiovascular Reserve Is Associated with Acute Kidney Injury after Intervention, European Journal of Vascular and Endovascular Surgery (2017), http://dx.doi.org/10.1016/j.ejvs.2017.01.014

serum creatinine (SCr) levels or estimated glomerular filtration rate (eGFR).[5]

Pre-existing renal disease,[6,7] diabetes, hypertension, smoking, cardiovascular disease, nephrotoxic medication, and contrast administration have been identified as common AKI risk factors.[2,6,8] Previous epidemiological analyses in patients undergoing cardiac intervention have also shown that history of myocardial infarction (MI), congestive heart failure, and reduced left ventricular ejection fraction are associated with post-operative renal decline.[10] Most of the risk factors associated with AKI in this setting are not modifiable, hence current prevention protocols focus predominantly on volume expansion or potentially protective pharmacological agents.[9] Cardiovascular reserve (CVR) is a parameter that is modifiable through various interventions. Estimation of CVR is increasingly being used to identify those at highest risk of complications after surgery.[11] Individuals with reduced CVR may be at higher risk of AKI because of an impaired physiological response to dehydration, hypovolaemia, and stress. There is no currently available literature investigating this association specifically in patients with peripheral arterial or aneurysmal disease, despite previous literature suggesting such an association in patients undergoing cardiac intervention.[10]

Alveolar oxygen uptake (VO_2) provides the arterial oxygen for delivery to contracting muscles reflecting the coupling of pulmonary gas exchange to cellular respiration. Above a certain work rate, exercise sustainability through aerobic regeneration of ATP is supplemented by anaerobic glycolysis resulting in production of lactic acid. The corresponding VO_2 at which lactic acid begins to accumulate defines the point of anaerobic threshold (AT), which can be measured by cardiopulmonary exercise testing (CPET); CPET provides an accurate estimate of CVR by measuring AT,[12] a reproducible marker of CVR, independent of patient effort.[13–17]

Patients undergoing repair of an abdominal aortic aneurysm (AAA) are at high risk of AKI.[1,8] Both open (OAR) and endovascular (EVAR) aneurysm repair can lead to significant renal insults.[18] Almost 20% of patients undergoing elective EVAR will develop AKI that is associated with impaired short and long-term outcomes.[1,2,8] Institutions are beginning to adopt CPET as a pre-operative risk assessment tool for patients undergoing EVAR. This provides a unique opportunity to assess a possible interaction between poor CVR and kidney injury in a population where pre-existing cardiovascular disease and AKI are common.

Therefore, the primary aim of this study was to assess the association between pre-operative CVR estimated through CPET and AKI following elective EVAR.

METHODS

Study population

This was a cohort study of patients undergoing elective EVAR for an infrarenal AAA between July 2009 and December 2015 in two tertiary centres. Data were collected prospectively using a database that was purpose built to investigate the effects of EVAR on renal function. Patients were eligible for repair if they had an AAA $>$ 5.5 cm or an AAA $<$ 5.5 cm with a rapidly increasing sac ($>$ 1 cm per year). Symptomatic, ruptured, infected or inflammatory AAAs or patients with end stage renal disease (ESRD) receiving dialysis were excluded. Written informed consent was obtained for the EVAR and data collection relating to this analysis. Appropriate ethics approval was granted by each institution. SCr measurements at baseline and at least 48 hours post-operatively, and cardiovascular comorbidities were collected. Overall, 448 patients undergoing elective EVAR were identified, of which 73 developed AKI. These 73 were case matched (1:3 ratio) to patients who did not develop AKI, based on pre-operative eGFR, calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) formula.[19–21] Since baseline eGFR as the main determinant of post-operative AKI after EVAR has been recently demonstrated,[6] case matching on the basis of eGFR values (within 5 mL/min/1.73 m^2) and age (within 3 years) was adopted.

Assessments

Participants underwent computed tomography angiography (CTA) with three dimensional reconstruction to assess anatomy; all contrast studies were performed at least 15 days prior to EVAR. Blood samples prior to EVAR were obtained before imaging or administration of contrast. A further sample was taken 24 and 48 hours after EVAR. Venepuncture to obtain the post-operative SCr measurement was timed to coincide with the 48 hours window specified by the definition criteria used in this study. This was performed by either a phlebotomist after the morning ward round (on a weekday or a Saturday), if that coincided with the 48 hours window, or a study team member if the venepuncture had to be performed later in the day or on a Sunday.

Definitions

To define and classify AKI, SCr measurements were used within 48 hours following EVAR, based on the "Kidney Disease Improving Global Outcomes" (KDIGO) criteria.[22,23] AKI was defined as an absolute increase in SCr of $\geq$ 0.3 mg/dL ($\geq$ 26.4 μmol/L), or a per cent increase $\geq$ 50% (1.5 fold from baseline), within 48 hours. This represents the patient meeting the minimum criteria for "Stage 1" AKI as per KDIGO definitions and National Institute for Health and Care Excellence (NICE) guidance.[24] For those who developed AKI (within 48 hours), further serial SCr measurements were obtained for at least 7 days. Patients were then classified into three stages. Stage 2 AKI was defined as 100–199% SCr rise within 7 days and Stage 3 as $\geq$ 200% SCr rise within 7 days or rise to $>$ 354 μmol/L with an acute rise $>$ 44 μmol/L. All patients in this study had a blood test 48 hours after the procedure.

Complications, comorbidities, and events were defined according to the reporting standards of Chaikof et al.[25] Hypercholesterolaemia was defined as a baseline total cholesterol $>$ 5 mmol/L. Hypertension was defined as the patient taking anti-hypertensives at recruitment or blood pressure $>$ 140/90 mmHg.

Please cite this article in press as: Saratzis A, et al., Pre-operative Functional Cardiovascular Reserve Is Associated with Acute Kidney Injury after Intervention, European Journal of Vascular and Endovascular Surgery (2017), http://dx.doi.org/10.1016/j.ejvs.2017.01.014