

Pre-Operative Functional Cardiovascular Reserve Is Associated With Acute Kidney Injury After Intervention

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What this paper adds

The impact of cardiovascular reserve on acute kidney injury (AKI) after endovascular surgery remains unclear, mostly due to the difficulties in assessing cardiovascular reserve. We are still unsure whether AKI is related mostly to pre-existing occult co-morbidities, such as cardiovascular disease, or procedure-related parameters. Hence, developing an adequate reno-protective strategy is not an easy task. In this analysis, we have shown that development of AKI after intervention is associated with pre-operative cardiovascular reserve, independent of other risk-factors and procedural parameters. This offers insight in what drives AKI development after endovascular intervention and where/how preventative measures should focus.

ABSTRACT

Background: Acute Kidney Injury (AKI) is a common complication after surgery or radiological intervention, associated with poor outcome over the short and long term. However, the mechanisms underlying AKI development remain poorly understood and the impact of pre-existing cardiovascular disease in procedure-related AKI is unclear; it remains unknown whether AKI is primarily related to pre-existing co-morbidity, mostly cardiovascular, or procedure-related parameters.

Methods: This is a case-control study; 292 patients undergoing elective endovascular 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/1.73m²) and age, to patients who had not developed AKI. Cardiopulmonary exercise testing (CPET) was used to assess cardiovascular reserve (CVR) using Anaerobic Threshold (AT). Development of AKI was defined using the Kidney Disease Improving Outcomes (KDIGO) guidance. We attempted to assess the association between CVR and AKI development using multivariate analysis.

Results: Pre-operative AT levels were significantly different between those who did and did not develop AKI (12±3 versus 15±3 ml/min/kg, $p<0.001$). 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% Confidence Interval (CI): 0.63-0.82, $p<0.001$], relative to AKI development. A pre-operative AT level <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, $p<0.001$). 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, $p < 0.001$).

Conclusions: Poor CVR was strongly associated with development of AKI. This provides pathophysiological insights into the mechanisms underlying AKI. Pre-operative CVR optimization may prevent renal injury in these individuals.

INTRODUCTION

Acute Kidney Injury (AKI) occurs in 13-18% of all hospital admissions and 20% of patients undergoing intervention (1-6). Development of AKI (7, 8) has been associated over both the short and long-term with increased rates of morbidity, hospital-stay, treatment-cost, and mortality(4, 5). This is independent of renal-function recovery, based on routinely used parameters such as serum-creatinine (SCr) levels or estimated glomerular filtration rate (eGFR)(9). Further to this, AKI is an important contributor towards development of Chronic Kidney Disease (CKD)(10). AKI-related treatment cost is significant; in the United Kingdom (UK) alone, AKI-treatment costs £620 million annually(11).

Several mechanisms have been implicated in intervention-related AKI pathophysiology(12) (13, 14). Pre-existing renal disease(15, 16), diabetes, hypertension(17), smoking, cardiovascular disease, nephrotoxic medication or contrast administration have been identified as common risk-factors (4, 14, 15). Most of these factors are not modifiable, hence current prevention protocols focus predominantly on hydration or administration of potentially protective pharmacological agents(18). Cardiovascular reserve (CVR) is a parameter that is modifiable through various interventions before non-urgent surgery. Estimation of CVR is increasingly being used to identify those at highest risk of complications after surgery (19-22). Individuals with reduced CVR may be at higher risk of AKI, due to impaired physiological response to dehydration, hypovolaemia, and stress. There is no currently available literature investigating this association.

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 circulating lactate begins to rise defines the point of Anaerobic Threshold (AT), which can be measured

by Cardiopulmonary Exercise Testing (CPET). The latter (CPET) is now being used frequently prior to major surgery (20-24). It provides an accurate estimate of CVR by measuring AT, a validated objective and reproducible marker of CVR, independent patient effort(25-29).

A typical population at high-risk for AKI is patients undergoing repair of an abdominal aortic aneurysm (AAA)(1, 14). Elective treatment in the form of open (OAR) or endovascular (EVAR) repair is advocated in those with an AAA of more than 5.5cm in diameter(30). Both OAR and EVAR can lead to significant renal insults (31). We have previously shown that almost 20% of patients undergoing elective EVAR will develop AKI and that is associated with impaired short and long-term outcomes(1, 4, 14). 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-existent 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 is a cohort study of patients undergoing elective endovascular repair (EVAR) of an infrarenal AAA between July 2009 and December 2015 in 2 tertiary centres. Data were collected prospectively. 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). EVAR was offered as a first-line procedure. 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 ethical approval was granted by each institution. Serum Creatinine (SCr) measurements at baseline and at least 48 hours and cardiovascular co-morbidities were collected. Overall, 448 patients undergoing elective EVAR were identified, of which 73 had 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 (32-34). Since we recently demonstrated that baseline eGFR is the main determinant of post-operative AKI after EVAR (15), we opted to case-match based on eGFR values (within 5 ml/min/1.73m²) and age (within 3 years).

Assessments

Participants underwent computed tomographic angiography (CTA) with 3-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.

Cardiopulmonary Exercise Testing (CPET) Protocol

Patients referred for elective AAA surgery at the main study centre (University Hospital Coventry and Warwickshire) undergo CPET as part of pre-operative risk-stratification. Resting spirometry is performed to measure forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), from which FEV1/FVC ratios are calculated; body-mass index (BMI) measurements were also obtained. Following that, FEV1 was used to predict an individual's maximum ventilation. Weight and predicted maximum oxygen uptake (VO₂max) were used to calculate the individually required work-rate on a cycle ergometer. Patients were subsequently attached to a 12-lead electrocardiogram (ECG) and a form-fitting face-mask connected to a metabolic cart with protocol-specific software (Viasprint Ergometer and MasterScreen CPX software, Care Fusion Corporation, CA, USA). Patients were initially made to pedal for an unloaded phase (work rate 0W at 50 rpm for 3 min) followed by a ramped phase requiring a constant 70 rpm against increasing resistance until they reached their peak oxygen uptake (VO₂peak). The test could be stopped at any point during the test protocol due to patient fatigue, presence of ischaemic ECG changes, chest pain or if the maximum heart rate was reached. The corresponding AT was derived using the V-slope method(35). An AT level of 11 ml/min/kg has traditionally been used as a threshold of sufficient CVR in various surgical and other clinical settings (27, 29, 36). Patients with an AT<11 ml/min/kg are not offered open surgical AAA repair in the institutions involved but will be considered for EVAR.

Definitions

In order to define and classify AKI, SCr measurements were used, within 48 hours after EVAR, based on the “Kidney Disease Improving Global Outcomes” (KDIGO) criteria (37, 38). AKI was defined as an absolute increase in SCr of more than or equal to 0.3mg/dl ($\geq 26.4 \mu\text{mol/l}$), or a % 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 of Health and Care Excellence” (NICE) guidance (39). For those who developed AKI (within 48 hours), further serial SCr measurements were obtained for at least 7 days. Patients were then classified into 3 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 $>354\mu\text{mol/l}$ with an acute rise $>44\mu\text{mol/l}$.

Complications, co-morbidities and events were defined according to reporting-standards by Chaikof et al (40). Hypercholesterolaemia was defined as baseline total cholesterol $>5\text{mmol/L}$. Hypertension was defined as patient taking antihypertensives at recruitment or blood-pressure $>140/90\text{mmHg}$.

Endovascular repair procedures

Procedures were performed under general anaesthesia, through vertical groin-incisions, using nonionic iodinated contrast medium (Iopromide). A device with suprarenal fixation modalities (Zenith, Cook Medical, Bloomington, Indiana, United States) was implanted, adhering to instructions for use (IFU). Prior to EVAR, the administration of contrast for at least 2 weeks and non-steroidal anti-inflammatory drugs (NSAIDs) for at least 1 week was avoided; metformin was discontinued for 2 days. For patients with a pre-operative $\text{eGFR} > 60 \text{ ml/min/1.73m}^2$, intravenous fluids (0.9% saline, 2mL/kg/hour) were started on the day of the operation. Patients with an $\text{eGFR} < 60$ units were admitted one day before and received intravenous fluids (0.9% saline, 2mL/kg/hour) for 12 hours. Urinary catheterization and hourly urine output measurements were routinely employed. Intra-operative fluid management was guided by mean arterial pressure (consisting only of crystalloid solutions), aiming to maintain it within 80% of the baseline for 90% of the operating time. Patients were asked to eat and

drink, as tolerated, as soon as possible. A blood transfusion was given if the patient's Haemoglobin (Hb) was less than 8g/dl or if the patient had a history of cardiac disease and was symptomatic with a Hb of less than 10g/dl. Patients were typically discharged on the 2nd post-operative day.

Follow-up

Patients were prescribed aspirin (75mg) and a statin (atorvastatin 40mg) when diagnosed with AAA, continued as life-long treatment. A standard follow-up protocol, including a clinical evaluation and biochemistry checks at 30 days, 6 months, 12 months, and annually thereafter, was used. Imaging during follow-up included plain abdominal radiography and an arterial duplex at 30 days, 6 months, 12 months, and annually thereafter. A computed tomographic angiography (CTA) was performed if evidence of a device-related complication was suspected. Type 2 endoleaks were treated conservatively(41, 42).

Statistical analysis

Analyses were performed using the Statistical Package for Social Sciences Version 21.0 (SPSS, Chicago, Ill, USA). Continuous parametric data are presented as mean value \pm standard deviation (SD) and categorical data are presented as absolute values and percentages. Comparisons between the study groups were performed using the independent or paired (where applicable) samples t-test for continuous parametric variables and Pearson's chi-square test for categorical variables. Following univariate comparison of relevant parameters between those with and without AKI, we entered variables with a p value <0.2 in a multivariate analysis using binary logistic regression in order to assess the effect of AT at baseline on AKI development. A Receiver Operating Characteristic (ROC) curve was calculated to assess the area under the

curve for AT as a predictor of post-operative AKI. A linear regression model was used to test association between AT and % change in SCr. A p value level <0.05 was considered statistically significant.

RESULTS

Overall, 292 patients were included, of which 73 had developed AKI and were case-matched (1:3 ratio) to 219 individuals who did not. None had excessive calcification, thrombus, or severe angulation at the proximal neck(40); none had a proximal neck length <10mm or renal artery stenosis. Table 1 summarizes main characteristics at baseline; the 2 groups were comparable in terms of most parameters known to influence AKI development. All AAAs were successfully excluded with no evidence of type 1 endoleak or occlusion of a main or accessory renal artery. None required a perioperative blood-product transfusion or stay in the intensive care unit. The amount of contrast administered during EVAR did not differ significantly between groups (130 ± 15 ml vs 125 ± 20 ml, $p=0.14$). None progressed to renal failure requiring dialysis. Of those who developed AKI, 64 were classified as stage 1, and 9 as stage 2.

The pre-operative AT and VO₂max levels were significantly different (univariate analysis) between groups (12 ± 3 versus 15 ± 3 ml/min/kg, $p<0.001$). 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% Confidence Interval: 0.63-0.82, $p<0.001$) (Tables 1 and 2). When entered into the same multivariate regression analysis as a dichotomous variable, a pre-operative AT level <11 ml/min/kg, a recognised cut-off point of cardiovascular fitness, was also associated with AKI development, with an OR of 7.8 (95% Confidence Interval: 3.75-16.51, $p<0.001$). The area under the curve (receiver operating characteristic analysis) for AT as a predictor of post-operative AKI was 0.81 (Standard Error: 0.06, 95% Confidence Interval: 0.69-0.93, $p<0.001$) – Figure 1. A linear regression model showed a possible association between AT levels at baseline and subsequent % change in SCr 48 hours after EVAR (correlation co-efficient: -0.731, $p<0.001$) – Figure 2.

282 patients had available eGFRs one year after the elective EVAR. For those with AKI, the eGFR drop was significant at 1 year ($p<0.001$) with an average drop of 3.5 ± 0.8 ml/kg/1.73m². For those without AKI, eGFR drop at 1 year was insignificant (average drop of 0.2 ± 0.7 units, $p=0.79$). For those with a baseline AT <11 ml/kg/min, eGFR dropped from 73 ± 11 ml/kg/1.73m² to 69 ± 14 ml/kg/1.73m² ($p=0.01$) at 1 year, whilst for those with a baseline AT ≥ 11 ml/kg/min, the drop in eGFR at 1 year was insignificant, from 67 ± 16 ml/kg/1.73m² to 66 ± 16 ml/kg/1.73m² ($p=0.09$). The number of endovascular re-interventions during the 1st post-operative year was not significantly different between the two groups (5.4% versus 4.9%, $p=0.76$).

DISCUSSION

To the best of our knowledge, this is the first study demonstrating an association between exercise AT, as an objective index of CVR and post-intervention AKI. This provides valuable mechanistical insights as to why these patients may develop AKI and provides useful information for potential AKI prevention strategies.

AKI is a sudden deterioration of renal-function, associated with increased mortality, morbidity, and healthcare-cost (5). A study involving 10,518 patients undergoing surgery suggested that long-term survival was worse those with AKI, even after complete eGFR recovery(43). We have previously shown a strong association between AKI after endovascular intervention, vascular surgery, renal transplantation or coronary angiography and subsequent short and long-term cardiovascular events and all-cause morbidity, in multiple cohort studies as well as a meta-analysis(4, 26, 28, 29). A recent review from NICE suggests that AKI has a major impact on safety and healthcare-cost (44); a patient with AKI after intervention spends an average of 4.7 extra nights hospitalised with an additional £3,691 for medical-treatment(5, 44). It is clear that procedure-related AKI is a major healthcare-issue.

The reasons why someone may develop AKI after surgery are multiple. Among these undergoing open vascular surgery, the renal injury appears to be mostly due to hypovolaemia, ischaemia-reperfusion injury or aortic cross-clamping(14) with an incidence between 10-20% for open aneurysm surgery. In endovascular surgery, contrast administration, renal microembolisation, coverage of renal arteries, lower-limb ischaemia and ischaemia-reperfusion syndrome, hypovolaemia, and pre-existent cardiovascular comorbidities have been implicated (14); however, most of these mechanisms are assumptive without supporting evidence, as we have previously discussed(14).

To the best of our knowledge, there has been no objective attempt to link AKI development and pre-procedural CVR. Exploring this association may provide pathophysiological insights into the mechanisms that underlie AKI development. It remains unknown whether development of AKI after surgery is primarily related to procedural risk-factors or whether it relates to occult pre-existing cardiovascular disease. (4) Those with reduced CVR are expected to respond sub-optimally to hypovolaemia, reperfusion injury and surgical stress, some of the common physiological insults in any form of vascular intervention. Hence, it is logical to assume that reduced CVR may amplify renal injury. Furthermore, CVR represents a modifiable risk-factor, through lifestyle interventions, medication and/or exercise(45, 46). Bearing these in mind, we sought to explore the relationship between AKI and CVR.

We chose a population of patients who undergo CPET prior to vascular surgery; CPET allows quantification of CVR during graded exercise. It accurately predicts the capacity to survive stress in various chronic conditions such as heart failure (47) as well as peri-operatively(19), by measuring AT levels. During CPET, exercise sustainability through the aerobic regeneration of ATP is supplemented by anaerobic glycolysis, resulting lactic-acid production. AT represents the upper limit of workload beyond which prolonged exercise is impossible(28). It has been shown to be an objective marker of CVR(19-22, 28). Patients undergoing EVAR have a high-prevalence of AKI risk-factors and are at significant risk of AKI (1, 14). Despite the fact that patients had multiple co-morbidities in our series, eGFR, a strong predictor of AKI (15), was well preserved and we case-matched based in baseline eGFR levels in order to compare balanced populations.

Our main finding is that AT level is associated with post-operative AKI. A decrease of a patient's AT by one unit translated to a 28% increase in chance of developing AKI ($p < 0.001$, adjusted analysis). Furthermore, CVR was associated with a decline in eGFR at 1 year; for

those with a baseline AT <11ml/kg/min eGFR dropped from 73 ± 11 to 69 ± 14 ml/kg/1.73m² (p=0.01).

Our findings have various implications. Firstly, this is, to the best of our knowledge, one of the first objective indications that AKI after vascular intervention relates to pre-operative cardiovascular status and not just procedure-related parameters. Hence, further to limiting the amount of contrast medium injected during endovascular manipulations and taking other steps to reduce the impact of the procedure itself to the kidney, prior cardiovascular optimisation may be important as part of AKI prevention. This may involve both lifestyle-related, as well as pharmaceutical interventions pre-operatively. Beta blocker use for example has been suggested as part of cardiac optimisation in vascular surgery (48). Targeted beta-blockade for those at highest risk and decreased CVR is an acceptable strategy but further RCT evidence is required. Those with reduced CVR may also benefit from pre-operative cardiac catheterisation/re-vascularisation. There is insufficient evidence to support the assumption that all vascular patients should undergo aggressive cardiac imaging and re-vascularisation; however, an RCT has shown that routine coronary angiography positively impacted long-term outcome of peripheral arterial disease surgical patients at medium or high risk(49). Other less invasive steps can be taken to optimise CVR in the community as well, such as smoking cessation, control of hypertension, weight-loss, correction of anaemia and diabetic control. High-intensity interval exercise may have a role (50). The precise interactions between patient and procedure related parameters leading to AKI development in surgery and endovascular intervention are definitely still not completely clear and further mechanistical evidence is required in that direction.

This study is limited by the number of participants. However, to our knowledge, it is the first study to attempt the use of such objective measures of CVR in patients prone to AKI. Some of the data relating to the EVAR procedures were also collected retrospectively, even though the

database was maintained prospectively. This study did not aim to collect long-term post-operative data for these patients, hence we cannot safely make associations regarding AKI, CVR and long-term post-operative course; we have previously investigated these in similar cohorts of patients(51). Finally, we cannot assess an association between severity of AKI and CVR, given that the vast majority of patients developed stage 1 AKI.

This study provides evidence that development of AKI after intervention is associated with pre-operative CVR, using objective measures, independent of other risk-factors and procedural parameters. Further validation is required in other surgical fields and future AKI prevention strategies cannot be unimodal and focus on procedure-related parameters only, but may have to include cardiovascular optimisation.

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TABLES

Table 1: Description of the groups with and without acute kidney injury after endovascular aneurysm repair (EVAR) – baseline characteristics

Variable	AKI	NO AKI	<i>P</i>
<i>n of participants</i>	73	219	-
Age, years	73±7	74 ±7	0.375
Male sex	67 (92%)	213 (97%)	0.080
Smoking	16 (22%)	38 (17%)	0.388
Hypertension	59 (81%)	165 (75%)	0.424
Asthma	8	35	0.263
COPD	14	52	0.590
Established heart failure	2	3	0.611
Prior CABG	9	31	0.572
Haemoglobin (g/L)	133±12	137±9	0.286
Contrast during EVAR (ml)	130±15	125±20	0.141
Cholesterolaemia	28 (38%)	72 (33%)	0.397
Stroke	3 (4%)	18 (8%)	0.303
MI	5 (7%)	26 (12%)	0.278
Diabetes	12 (1%)	31 (14%)	0.703
ACE-inhibitor therapy	27 (37%)	84 (38%)	0.890
Angiotensin receptor blocker therapy	10 (14%)	39 (18%)	0.474
Antiplatelet therapy	65 (89%)	173 (79%)	0.057
Diuretic therapy	37 (51%)	109 (50%)	1.000
NSAID therapy	3 (4%)	8 (4%)	1.000
Statin therapy	60 (82%)	175 (80%)	0.736
AT, ml/min/kg	12±3	15±3	<0.001
Baseline eGFR, ml/kg/1.73 m ²	68 ±16	68 ±15	0.765
FEV1, litres	2.2±0.7	2.4±0.7	0.046
% VO ² max	73±17	82±19	0.001
AT <11 ml/min/kg	33 (45.2%)	19 (8.7%)	<0.001

AKI: Acute Kidney Injury

COPD: Chronic Obstructive Pulmonary Disorder

CABG: Coronary Artery Bypass Grafting

MI: Myocardial Infarction

ACE: Angiotensin Converting Enzyme

NSAID: non-steroidal anti-inflammatory drug

AT: Anaerobic Threshold

eGFR: estimated Glomerular Filtration Rate

FEV1: Forced Expiratory Volume in 1 second

Table 2: Serum Creatinine (SCr) and estimated Glomerular Filtration Rate (eGFR) measurements for the 2 groups

	Baseline SCr	48 hours SCr	Baseline eGFR	1 year eGFR
AKI	95.4±25	155.9±42	67.8±16	64.3±18
No AKI	92.9±11	102.8±15	68.4±15	67.9±14
<i>p</i>	0.59	<0.001	0.76	0.13

SCr in $\mu\text{mol/l}$

eGFR in ml/min/1.73m^2

Table 3: Multivariate analysis of the associations of baseline risk-factors on post-operative development of acute kidney injury

Parameter	<i>p</i>	OR	95% Confidence interval	
Male sex	0.02	0.13	0.04	0.50
Antiplatelet therapy	0.18	1.82	0.76	4.30
FEV1	0.23	0.77	0.50	1.18
% VO2 max	0.70	0.99	0.98	1.01
AT	<0.001	0.72	0.63	0.82

OR: Odds Ratio

MI: Myocardial Infarction

FEV1: Forced Expiratory Volume in 1 second

AT: Anaerobic Threshold

FIGURE LEGENDS

Figure 1: Receiver operative characteristic (ROC) curve for anaerobic threshold as a predictor of post-operative acute kidney injury (AKI) - area under the curve: 0.81 (Standard Error: 0.06, 95% Confidence Interval: 0.69-0.93, $p < 0.001$)

Figure 2: Scatter-plot showing the association between anaerobic threshold at baseline (x-axis) and % change in Serum Creatinine (SCr) 48 hours after endovascular aneurysm repair (linear regression)