Impact on Renal Function after Endovascular Aneurysm Repair with Uncovered Supra-renal Fixation Assessed by Serum Cystatin C

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Objective. Supra-renal fixation in endovascular aneurysm repair (SR-EVR) is used to improve the proximal seal of aortic stent grafts and appears to have minimal effect on serum creatinine. Serum cystatin C (CC) is a more sensitive marker of renal injury and, unlike creatinine, is unaffected by non-renal influence. The aim of this study was to assess the true renal effect of SR-EVR using this superior renal index.

Methods. Consecutive patients undergoing SR-EVR were prospectively recruited and compared to control groups undergoing open aneurysm repair (OR) and colorectal resection (CR). Serum CC and creatinine clearance (CrC) were determined pre-operatively and at 3, 6 and 12 months post-surgery. Renal function was compared using analyses of covariance (ANCOVA).

Results. Sixty-five patients (M:F; 52:13, median age 74 years) were enrolled (24 SR-EVR, 28 OR, 13 CR). Pre-operative renal function and risk factors were comparable (CC 1.04 mg/l, SR-EVR; 0.96 mg/l, OR; 0.97 mg/l, CR). Adjusting for baseline renal function, there was no significant difference in CC or CrC between study and both control groups at 3, 6 or 12-months post-operatively.

Conclusion. Using cystatin C as a more sensitive renal index, there was no detectable evidence of kidney dysfunction at up to one-year following EVR with uncovered bare-metal supra-renal fixation.

Keywords: AAA; Endovascular repair; Supra-renal fixation; Trans-renal fixation; Renal function; Cystatin C.

Introduction

Contemporary opinion supports the use of uncovered bare metal supra-renal (SR) fixation in devices for endovascular repair (EVR) of abdominal aortic aneurysm (AAA) for improved longer-term stent-graft durability. Some authors have also suggested that this practice may also serve to increase anatomical eligibility for EVR due to a reduction in the prohibitive proximal neck morphology observed in many cases.

Several uncontrolled studies have now been published assessing the safety of bare metal supra-renal fixation following SR-EVR. Although there is no current evidence of any adverse renal effect, biochemical renal assessment has relied almost exclusively on blood urea nitrogen (BUN) and serum creatinine (sCr) methods. More recently, the low molecular weight protein cystatin C (CC) has been validated as a superior endogenous renal marker to sCr that may enable the detection of sub-clinical renal injury.

Using this more sensitive renal index (serum CC), the aim of this study was to prospectively compare renal function in SR-EVR patients with conventional open AAA repairs (OR) and others undergoing laparotomy for non-vascular pathology.

Patients and Methods

This was a prospective, controlled trial of patients undergoing elective AAA repair at a major tertiary referral centre over a twelve-month period commencing May 2002. Full ethical approval was obtained and all patients were issued relevant information sheets with appropriate consent documentation prior to inclusion.

During the study period, all AAA patients undergoing elective aortic repair were considered for study...
inclusion. Suitable patients with anatomically eligible pathology were randomized as per EVAR-1 trial protocol to either EVR (study group) or OR (control group). Consecutive primary endovascular repairs and open AAA repairs performed outside EVAR-1 supplemented the EVR and OR limbs respectively. In addition, another sequential but limited control series of patients undergoing resection for colorectal malignancy (CR) was also recruited. Pre-operative renal failure with a requirement for renal replacement therapy (i.e. haemo- or peritoneal dialysis) precluded study inclusion.

At study enrollment, patient factors recorded included sex, age, weight, smoking habit, maximal antero-posterior AAA neck and sac sizes (calibrated on CT scan) and medical co-morbidity. The pre-operative differential renal function in all patients undergoing AAA repair (EVR & OR) was assessed by radio-labelled DTPA (Diethylene Thiamine Penta-acetic Acid) scanning. EVR-related procedural variables recorded included device type, deployment success and radiological contrast load.

All patients were reviewed at follow-up intervals of 3, 6 and 12 months. Biochemical markers of renal function were recorded pre-operatively and at these specific time points. Serum creatinine (sCr) and cystatin C (CC) were measured. The Cockroft-Gault formula was used for determination of glomerular filtration rate (GFR).

Results

Sixty-five patients were recruited to the trial in the 12-month study period. Of these, 52 participants required elective AAA repair (24 EVR and 28 OR) whereas the remaining 13 underwent planned laparotomy for major colorectal resection (CR).

Twenty-two of the 52 AAA patients were randomized as part of the EVAR-1 trial (12 EVR & 10 OR). The remaining 30 cases were therefore primary aortic repairs (12 EVR and 18 OR). Primary EVR stents were preferred for AAA repair in the setting of a hostile abdomen. Regarding the 18 primary OR patients outside the EVAR-1 trial, 4 eligible patients refused EVAR-randomization, 2 patients were <60-years old and 12 cases were morphologically unsuitable (short neck (n = 7); mural thrombus (n = 3) and excessive angulation (n = 2)).
For those patients presenting for AAA repair (EVR and OR), maximal antero-posterior sac and neck sizes were comparable (as per calibration for EVAR-1 trial). There were three cases of inflammatory AAA: one patient underwent ‘primary’ EVR following failed OR and the other two were randomized to the OR limb as part of EVAR-1. One aortic repair was performed for a symptomatic (non-ruptured) 44 mm AAA in a 52-year old patient with a strong family history of aneurysm rupture.  

Peri-Operative Factors & Early Outcome

Two different types of supra-renal fixed endovascular stent were used in the study group. Thirteen patients received the Zenith device (Cook Inc., Bloomington, Ind.) with the other 11 cases undergoing EVR using the Cordis system (Johnson & Johnson, Miami, Florida). Median radiological contrast load (300 mg Iodine/ml) during endovascular repair was 163 ml (range 110–350 ml).

Stent-graft implantation was technically successful with satisfactory completion imaging in all but one case (‘Patient 11’). Despite correct positioning prior to deployment, the Zenith device encroached on the left renal artery ostia with the covered segment of stent after release. The right renal artery appeared unaffected. Oliguria was noted as early as the theatre recovery room and this was unresponsive to aggressive guided (CVP) fluid resuscitation, frusemide and mannitol. Poor renal function was confirmed on an early post-operative DTPA scan, as the patient gradually became anuric, fluid overloaded and acidotic. This resulted in permanent haemo-dialysis dependence by the third post-operative day.

No early renal complications were observed in either of the control groups. Temporary supra-renal aortic cross clamping was required in 2 open AAA repairs in order to gain proximal control. In both of these cases there were no associated adverse renal sequelae.

The one early death of the entire series followed the primary EVR of a 76 mm AAA in a patient with known myelo-proliferative disorder and massive splenomegaly. Initially, his post-operative progress appeared satisfactory and he was actually discharged for further convalescence at day 6. Re-admitted two days later with sudden back pain, an urgent CT scan demonstrated no stent-related problem. Within a week though, he had developed severe chest sepsis and a consumptive coagulopathy (DIC) that was ultimately responsible for his demise from multi-organ failure.  

Late Outcome & Delayed Renal Function

Follow-up, Device Failure & Late mortality

Excluding late mortality, twelve-month follow-up was complete in all but one OR patient (dropout rate <0.5%). He withdrew for personal reasons at Table 1. Pre-operative Patient & AAA-related factors

<table>
<thead>
<tr>
<th></th>
<th>EVR (n=24)</th>
<th>OR (n=28)</th>
<th>CR (n=13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74 (64–83)</td>
<td>75 (52–87)</td>
<td>72 (61–86)</td>
<td>0.86*</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>21:3</td>
<td>23:5</td>
<td>8:5</td>
<td>0.59†</td>
</tr>
<tr>
<td>Co-Morbidity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic Heart Disease</td>
<td>12 (50)</td>
<td>11 (39)</td>
<td>5 (38)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (46)</td>
<td>15 (54)</td>
<td>6 (46)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6 (25)</td>
<td>4 (14)</td>
<td>2 (15)</td>
<td>0.33</td>
</tr>
<tr>
<td>Renal Impairment (no RRT)</td>
<td>4 (17)</td>
<td>5 (18)</td>
<td>2 (15)</td>
<td>0.31</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>6 (25)</td>
<td>8 (29)</td>
<td>5 (38)</td>
<td>0.95</td>
</tr>
<tr>
<td>Renal Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCr (Range)/µmol⁻¹</td>
<td>110.5 (78–211)</td>
<td>110.5 (86–174)</td>
<td>100.5 (70–178)</td>
<td>0.99†</td>
</tr>
<tr>
<td>CrC (Range)/mlmin⁻¹</td>
<td>62 (38–89)</td>
<td>55 (25–92)</td>
<td>62 (22–82)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cystatin C (Range)/mgl⁻¹</td>
<td>1.04 (0.3–2.01)</td>
<td>0.96 (0.34–1.78)</td>
<td>0.97 (0.39–2.11)</td>
<td>0.55</td>
</tr>
<tr>
<td>Radiological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Renal Size (IQR)/mm</td>
<td>100 (20)</td>
<td>100 (14)</td>
<td>-</td>
<td>0.61</td>
</tr>
<tr>
<td>% Function Right Kidney</td>
<td>0.53 (0.02)</td>
<td>0.54 (0.03)</td>
<td>-</td>
<td>0.82‡</td>
</tr>
<tr>
<td>Aneuysmal Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sac Size (Range)/mm</td>
<td>62 (55–85)</td>
<td>63.5 (44–103)</td>
<td>-</td>
<td>0.14</td>
</tr>
<tr>
<td>Neck Size (Range)/mm</td>
<td>22.5 (18–26)</td>
<td>21 (17–26)</td>
<td>-</td>
<td>0.22</td>
</tr>
<tr>
<td>Neck Length (Range)/mm</td>
<td>26.5 (14–48)</td>
<td>27 (16–30)</td>
<td>-</td>
<td>0.48‡</td>
</tr>
<tr>
<td>Inflammatory AAA</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Symptomatic AAA</td>
<td>0</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* ANOVA; † chi²; ‡ 2 sample t-test.

(defined as a ‘screening’ sCr value beyond the limits of the normal reference range) were not excluded.

For those patients presenting for AAA repair (EVR and OR), maximal antero-posterior sac and neck sizes were comparable (as per calibration for EVAR-1 trial). There were three cases of inflammatory AAA: one patient underwent ‘primary’ EVR following failed OR and the other two were randomized to the OR limb as part of EVAR-1. One aortic repair was performed for a symptomatic (non-ruptured) 44 mm AAA in a 52-year old patient with a strong family history of aneurysm rupture.
10 weeks during a period of prolonged rehabilitation following open aortic surgery.

Secondary re-intervention for device failure had been required in only one EVR patient at 1-year follow-up. In this case of initially uncomplicated Zenith deployment, the pre-discharge CT scan revealed evidence of a distal attachment site endoleak that was managed successfully by endovascular limb extension. Unfortunately, the same patient required repair of the access artery pseudo-aneurysm one month later but has had no further problems since.

Only one of the five late deaths was due directly to the presenting primary surgical pathology, whose late follow-up is detailed below. Another EVR patient died at 6-months from pancreatic cancer which was not apparent on initial radiological studies. There were two late deaths due to myocardial infarction occurring at three (CR) and nine-months (OR) post-operatively. Finally, one other CR patient expired at 6-months because of a cerebro-vascular accident.

### Biochemical Renal Function
Change in renal function at specific time intervals (3, 6 and 12-months) for each of the groups is shown in the box-and-whisker plots of both Figs. 1 (CrC) and 2 (CC). The annual median (IQR) change in CrC from baseline was \(-2.1 (5.7) \text{ ml/min}^{-1}\) following EVR compared to \(-3.1 (8.4) \text{ ml/min}^{-1}\) for OR and \(-4.6 (12.1) \text{ ml/min}^{-1}\) for CR. Similarly, at this follow-up time there appeared to be no significant incremental difference in CC between groups with a median CC change from baseline of \(+0.33 (0.22) \text{ mg/l}^{-1}\) after EVR and \(+0.28 (0.54) \text{ mg/l}^{-1}\), \(+0.25 (0.74) \text{ mg/l}^{-1}\) for OR and CR respectively.

There was only one significant renal complication in the study that concerned Patient 11 of the study limb who developed significant dialysis-dependant renal compromise after device deployment inadvertently occluded the left renal artery during EVR. At 6-month review this was reflected biochemically by a fall in CrC to 13.4 mlmin\(^{-1}\) (65 mlmin\(^{-1}\) pre-op) and a concomitant rise in CC to 5.96 mg/l\(^{-1}\) (1.62 mg/l\(^{-1}\) pre-op). Interestingly, although the early DTPA scan confirmed hypoperfusion, both kidneys did in fact enhance. A renal duplex study (Day 8 post-EVR) confirmed this bilateral kidney perfusion, albeit significantly reduced on the left side (absent spectra). Also unexpected was the presence of cortical enhancement of both kidneys on a satisfactory routine post-EVR CT scan. Despite discharge home this patient required multiple re-admissions with problematic fluid status and cardiac arrhythmias secondary to electrolyte imbalance, before dying at 8-months post-EVR with end-stage renal failure. No other patient in EVR, OR or CR required renal replacement therapy for any indication during the entire study period.

### Radiological Renal Analysis
The one-year follow-up CT images for both the EVR and relevant OR cases were each compared to their pre-operative scans. Follow-up imaging was not performed in the 3 EVR patients who died within 1-year and considered incomplete (entire organ not visualized) in four patients. Forty EVR and 20 OR kidneys were therefore available for analysis.

There were two new isolated renal infarcts identified in the EVR group (8.3%) as opposed to none in those who underwent open AAA repair. Neither case was however accompanied with clinical or biochemical evidence of renal dysfunction. At annual follow-up bipolar renal size had not changed significantly from pre-operative values in either group (paired t-test).
Median (IQR) EVR bipolar size was 100 (15) mm (pre-op 100 (20) mm) and mean OR size 100 (18 mm (pre-op 100 (14) mm).

Discussion

Since the seminal paper of Malina et al., several groups have attempted to resolve the concerns of potential renal effect following EVR with uncovered bare metal supra-renal fixation. Unfortunately, these early reports involved study groups of trans-renal EVR patients without control subjects for comparison and further evaluation of any fixation-specific renal outcome was clearly required.

In 2002, Krämer et al. published the first report of fixation-specific renal outcome following EVR. In the study, which was not concerned with biochemical renal function, the post-operative CT images of 99 EVR patients (both IR and SR) were reviewed at a minimal follow-up of 12 months. Supra-renal fixation was found not to be associated with an increased incidence of renal infarcts post-EVR compared to endografts secured entirely with infra-renal fixation.

Soon after, the Montefiore group reported comparative renal outcome in 130 EVR (69 SR) patients with a mean follow-up of 17 months. There was a significant increase in sCr from pre-operative values in both groups, yet no incremental difference between fixation-type was observed. Similarly, CrC (Cockroft-Gault) was significantly reduced for both SR and IR-fixed EVR, but the extent of this fall was no different between study limbs. Post-operative renal dysfunction (defined as sCr increase > 0.5 mg/dl above baseline) developed in 10.7% (14/130) with again no difference observed between groups.

Lau et al. also described an increase in sCr following both IR and SR-EVR in their series of 89 patients. Although this was quoted to be statistically significant at 1-year in the IR (and not the SR) group, the elevated median sCr remained within the normal reference range and group specific CrC values were unaffected. The clinical implications of these findings are unclear.

These reports and a review of the literature indicate a common reliance on the use of insensitive sCr methods in order to assess biochemical renal function. There are several inherent limitations with this approach. Firstly, sCr is formed by the non-enzymatic conversion of muscle creatine and phosphocreatine and hence its production rate is unstable, under direct influence from many non-renal factors (e.g. dietary preference, sex, muscle mass and surgical intervention). The Cockcroft-Gault formula attempts to correct for these variables in the expression for creatinine clearance. Regardless, the glomerular filtration rate (GFR) may still have to fall by at least 50% before reflected in an elevated sCr (and reduced CrC). Finally, laboratory quantification of sCr is usually based on the Jaffe reaction, a colorimetric assay with complex-formation between creatine and alkaline picrate (‘Janovsky complex’). Unfortunately, other chromogens are present in plasma leading to falsely high levels of sCr e.g. uric acid, ketones, glucose and plasma proteins. Serum cystatin C is generally accepted as a better marker of excretory renal function. The low molecular weight protein is produced by all nucleated cells, is unaffected by sex or muscle mass and is freely filtered and metabolised in the kidney. It has been extensively validated by correlation with the gold-standard measurements of GFR (i.e. inulin clearance, iohexol and 51Cr-EDTA) and typically reported superior to sCr in this respect.

Furthermore, CC appears more sensitive in signifying earlier reductions in GFR (25–30%) and therefore renal injury at a level that may be currently undetected in those EVR patients with supra-renal stent systems. This study is not the first to employ CC as a sensitive renal index post-EVR. Aho et al. compared the short-term renal outcome of 15 EVR patients to OR controls using CC, sCr and CrC as markers of renal excretory function. This study found evidence of increased glomerular filtration in both groups in the early post-operative phase. Conversely, EVR did not protect from proximal tubular damage in either group (increased urinary N-acetyl-beta-D-glucosaminidase (NAG) to creatinine ratio) despite no patient developing clinical evidence of renal impairment. Our study assessed only the excretory (glomerular) component of organ function since this is reported to offer the best clinical estimate of functional renal mass, correlating well with the severity of any observed renal dysfunction. Over a longer 12-month follow-up period using cystatin C, we have found no evidence suggestive of significant renal impairment in those patients undergoing SR-EVR, conventional open AAA repair or laparotomy for colorectal resection. Admittedly, in view of the relatively small number of patients included in the study, its power is must be taken in context. Furthermore, the unavoidable use of two specific differing endograft designs within the study group may act as a source of bias. Nevertheless, the findings should promote further confidence in those advocating SR-EVR in the management of AAA.

Although there was no formalized renal protection policy within our unit, all patients with renal impairment (abnormally elevated sCr without a requirement

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for RRT) underwent careful intravenous fluid optimi-
zation with routine urinary catheterisation and central
venous monitoring where appropriate. If possible, the
administration of any contrast agent prior to EVR
(within 2 weeks) was avoided and the procedural vol-
ume used during EVR was restricted to the absolute
minimum required. Although it was not the policy
of the unit to routinely prescribe putative ‘reno-
protective’ agents such as dopexamine or mannitol,
a peri-operative intravenous infusion was commenced
if clinically indicated.

A specific intra-operative measure taken to mini-
mize renal injury was the angiographic imaging of
the renal arteries following partial stent deployment
(Fig. 3a). This was an attempt to confirm correct device
positioning (Fig. 3b) prior to complete release in order
to reduce the risk of renal artery compromise by the
covered segment of the stent. Unfortunately, the prac-
tice was not entirely failsafe and we describe in detail
the single case of the series with inadvertent deploy-
ment error (Patient 11). This case was particularly in-
teresting since the exact cause of renal failure was
essentially unknown. Initially, the encroachment of
the device on the left renal artery ostium at deploy-
ment was blamed for the acute renal failure (Fig. 3c).
Simple organ ischaemia alone cannot fully explain
the clinical deterioration since DTPA, renal duplex
and CT scanning revealed evidence of a maintained
(albeit impaired) bilateral renal perfusion. Perhaps
this reflected an initial patent renal collateral circula-
tion that was insufficient to maintain adequate renal
function. Cholesterol embolization could have also
played a role but this remained unproven as no renal
biopsy was performed and a post-mortem refused.

The incidence of renal infarcts in the study post-
EVR was comparable to the 8.3% reported by Kramer
et al.16 One case could plausibly be explained by the
intentional deployment of covered EVR stent over
a small accessory renal artery that was identified on
pre-operative imaging. The second instance most
likely occurred due to the embolism of debris present
in the region of the AAA neck during endograft
manipulation and deployment. In several other cases
there were transient procedural territorial renal
infarcts but all had completely resolved by 12-month
follow-up. Fortunately, both persistent cases were
clinically insignificant and not associated with any
biochemical renal derangement. Cayne et al. reported
a similar functional indifference to renal infarction
(using sCr and CrC methods) present in 5.8% of their
130 EVR cases.17

Renal failure following endovascular AAA repair is
generally considered multi-factorial in origin, occur-
rning in 6% of patients with normal pre-operative kid-
ney function. The longer-term CC data yielded by
this prospective work supports the hypothesis that
EVR devices with uncovered bare metal suprarenal
fixation have no detrimental effect per se on renal
function at up to 1-year post AAA repair. Indeed, con-
trary to the suspected negative impact of trans-renal
EVR these stents may actually in fact be protecting
patients from late renal failure courtesy of improved

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Fig. 3. Patient 11: Intra-operative imaging. (a) Pre-deployment angiogram: device positioned too cranially, (b) Device appro-
priately withdrawn: covered segment apparently below renal arteries, (c) Completion angiogram: device mal-deployment
with occlusion of left renal artery (splenic artery visible).
device durability and hence a reduced requirement of remedial secondary interventional procedures, each with its own potential contrast-induced nephrotoxic insult.

References


