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Oxygen Free Radical and Cytokine Generation During Endovascular and Conventional Aneurysm Repair

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Objectives: *Endovascular aneurysm repair has been proposed as a "minimally invasive" alternative to conventional aneurysm resection. One of the most important potential benefits of endoluminal surgery is the avoidance of aortic cross clamping, which may attenuate the ischaemia - reperfusion injury that complicates open aneurysm repair. This study aimed to quantify the metabolic response to both conventional and endovascular aortic surgery.*
Design: *Prospective clinical study.*
Setting: *University hospital.*
Methods: *Femoral vein blood samples (pre-clamp, during aneurysm repair and 5 and 30 min post reperfusion) were obtained from 12 patients undergoing aortoaortic aneurysm repair, six by conventional transperitoneal inlay replacement (median age 71 years, median aneurysm diameter 5.8 cm), and six by endoluminal deployment of a straight endograft (median age 73 years, median aneurysm diameter 5.5 cm). All endovascular procedures were completed satisfactorily with no conversions to conventional surgery.*
Outcome measures: *Venous blood samples were analysed for oxygen free radical (OFR) production using the quantifiable oxidation of IgG in plasma, and cytokine (IL-1β and TNF-α) generation by radioimmunoassay.*
Results: *The results are given as median values with interquartile ranges:*

	Peak Levels (change from baseline)		
	OFR	IL-1β	TNF-α
Conventional repair	1.93 (1.4–2.0)	1.42 (0.74–2.03)	1.23 (0.39–1.34)
Endovascular repair	1.55 (1.33–1.92)	1.02 (0.56–1.1)*	0.81 (0.66–0.96)*

*$p < 0.05$ - two way analysis of variance

Conclusions: *These results suggest that the ischaemia - reperfusion response associated with conventional aneurysm surgery may be largely negated by endovascular techniques. This may have significant consequences as the generation of oxygen free radicals and cytokines have been implicated in the development of systemic organ failure following aortic surgery.*

Key Words: Endovascular aneurysm repair; Ischaemia - reperfusion injury; Oxygen free radicals; Cytokines.

Introduction

Endovascular aneurysm repair involves the intraluminal placement of a graft-stent combination within an infrarenal abdominal aortic aneurysm (AAA). The endograft is usually introduced from a remote arterial site, and is positioned to exclude the aneurysm from the circulation, with the aim of promoting intra-aneurysmal thrombosis and eliminating the risk of rupture.

The two principle theoretical advantages of endovascular aneurysm repair are the avoidance of intra-abdominal manipulation, and the absence of aortic clamping. Conventional exposure of the infrarenal aorta necessitates a large abdominal incision, mobilisation of the abdominal viscera and retroperitoneal dissection. These procedures are associated with predictable complications,[1] which may be reduced by endovascular repair.

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Infrarenal aortic clamping during conventional aneurysm repair is associated with a fall in cardiac stroke volume and a rise in left ventricular end diastolic volume[2–4] which may be responsible for cardiac related mortality. Unclamping the aorta and subsequent reperfusion, initiates the generation of oxygen free radicals which have been implicated in the development of multiple organ failure.[5–9] During endovascular repair, the aorta is not clamped, although it may be temporarily occluded by devices using balloon inflation during stent deployment. The reduction or absence of aortic occlusion in endovascular repair has the potential to diminish the severity of the ischaemia-reperfusion syndrome and its associated systemic consequences.

Since its inception, endovascular aneurysm surgery has been adopted by many surgeons who have demonstrated its technical feasibility.[10–15] However despite this enthusiasm, initial clinical reports have documented relatively high complication rates, and proof of the expected benefits from endovascular repair are lacking. This study investigated the effect of intraluminal techniques on ischaemia-reperfusion injury, by quantifying oxygen free radical and cytokine generation in a non-randomised cohort of patients undergoing conventional and endovascular aneurysm repair.

Methods

Patient cohort

In our unit, all patients with AAAs greater than 5.5 cm in diameter are assessed with MRI angiography, contrast enhanced CT-scanning and colour Duplex imaging.[16] Patients who fulfil the criteria for endovascular repair are scheduled for tube or tapered reconstruction, whilst those patients unsuitable for endoluminal surgery undergo conventional repair. The morphologic requirements for straight endograft reconstruction, necessitate an aneurysm confined to the infrarenal aorta with a proximal neck of at least 1.5 cm, a distal neck of 1 cm, and an iliofemoral segment of sufficient calibre to accommodate a 23F sheath.[17]

The patient cohort for this study comprised 12 patients undergoing aorto-aortic grafting for AAA, six by conventional transperitoneal operation, and six by endovascular repair. The details of each group of patients are presented in Table 1.

All operations were performed under general anaesthesia, without epidural opiates or local anaesthetic. Patients were induced with thiopentone and

Table 1. Table illustrating patient demographics. Continuous variables are presented as median values with ranges in parenthesis

	Endovascular repair (n=6)	Conventional repair (n=6)
Age	72.5 (64–76)	71 (64–85)
Sex (M/F)	6/0	3/3
Hypertension	3	1
IHD	4	0
PVD	3	1
Current smokers	1	3
Aneurysm diameter	5.5 (5–6.2)	5.8 (4.4–7.6)
Aortic clamp time (min)	–	35 (20–60)

IHD: ischaemic heart disease; PVD: peripheral vascular disease.

received a balanced general anaesthetic of nitrous oxide, oxygen, isofluorane and morphine. Sodium nitroprusside was utilised to reduce cardiac afterload where indicated,[18] and substances with known antioxidative properties were avoided during the perioperative period.[19]

Operative details

Conventional repair was undertaken transperitoneally, using an inlay technique.[20] All patients in this trial underwent tube repair, with cranial cross-clamping below the renal arteries and distal control of the common iliac arteries.

Endovascular repair was performed using the Endovascular Technologies EGS system as has been described previously.[10] Briefly, this system consists of a straight dacron prosthesis anchored with a cranial and caudal modified Z-stent. The stents are self expanding, but each is opposed to the aortic wall with a limited balloon inflation. During the procedure, the aorta was occluded for 1 min duration on four separate occasions (two proximal and two distal balloon inflations). The endograft was placed via the common femoral artery in two cases and through a temporary iliac conduit in the remaining four.[21] All patients had a straight endograft successfully placed, with no open conversions in the trial group. No intraoperative complications were encountered in either group.

All patients consented to inclusion in the trial which was approved by our local ethical committee.

Free radical and cytokine assays

In both groups of patients, venous blood samples were obtained from the common femoral vein following

Table 2. Table illustrating cytokine and free radical results. Values are medians with interquartile ranges in parenthesis

	Baseline	Proximal anastomosis	Distal anastomosis	5 min reperfusion	30 min reperfusion
OFR-EV	0.45 (0.38–0.88)	0.64 (0.52–1.1)	0.67 (0.48–1.43)	0.71 (0.5–1.24)	0.68 (0.48–1.24)
OFR-Con	0.6 (0.48–1.0)	0.96 (0.51–1.25)	1.06 (0.51–1.38)	1.14 (0.89–1.51)	1.13 (0.92–1.37)
IL-1β-EV	2.4 (2.37–3.25)	2.56 (1.3–3.52)	2.65 (1.9–3.3)	2.1 (1.35–3.68)	2.3 (1.8–3.37)
IL-1β-Con	1.7 (1.27–2.5)	1.45 (1.2–1.83)	2.1 (1.65–3.4)	1.82 (0.69–2.13)	2.5 (1.52–2.8)
IL-6-EV	0.32 (0.26–1.15)	0.44 (0.21–0.97)	1.12 (0.1–2.38)	1.2 (0.14–1.25)	1.15 (0.79–2.65)
IL-6-Con	0.12 (0.1–0.25)	0.16 (0.12–0.52)	0.12 (0.1–1.36)	0.15 (0.1–0.54)	0.22 (0.1–0.61)
TNF-α-EV	10.3 (4.5–14.1)	5.8 (3.8–13.1)	3.9 (2.1–10.4)	4.4 (1.5–11.6)	5.25 (4.0–9.8)
TNF-α-Con	3.35 (2.1–4.7)	5.05 (3.4–8.6)	4.75 (3.3–10.9)	4.3 (1.8–6.8)	5.25 (3.6–7.7)

OFR: oxygen free radicals; IL: interleukin; TNF: tumour necrosis factor; EV: endovascular repair; Con: conventional repair.

induction of anaesthesia, prior to aortic clamping or balloon occlusion, during completion of the proximal and distal anastomoses (sutured or stented), and at 5 and 30 min following reperfusion. Samples were centrifuged at 3000 rpm for 5 min, and plasma snap frozen in liquid nitrogen for later analysis. In the endovascular group, blood was obtained from the common femoral vein contralateral to the insertion site.

Production of oxygen free radicals was indirectly measured by the method of Lunec *et al.*,[22] utilising the quantifiable oxidation of IgG in plasma. Cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) were quantified by commercially available radioimmunoassay (Amersham International plc, Bucks, U.K.). The sensitivity of these assays was given as 38pg/ml, 22pg/ml and 90pg/ml respectively.

Statistical analysis

Results are presented as medians with interquartile ranges. Analysis of the data groups utilised a two-way analysis of variance with significance at the 95% level. Two-way analysis of variance was assumed to be significant when the observed F value (F_{ob}) exceeded the critical F value (F_c).[23]

Results

The absolute values for cytokine and free radical generation are tabulated in Table 2. The proportional change from control, baseline values for both cytokine and free radical species are illustrated in Figs 1–4.

Interleukin-1β, TNF-α, and free radical production were increased over baseline values during conventional aneurysm repair. These changes in IL-1β, TNF-α, and free radical generation were reduced by endovascular aneurysm repair when compared to conventional procedures. The reduction in IL-1β and TNF-α was significant at the 95% confidence level

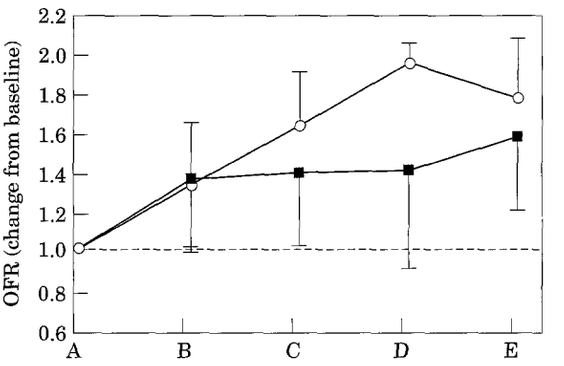

Fig. 1. Graph illustrating the changes in oxygen free radical (OFR) generation during endovascular (■) and conventional aneurysm (○) repair. Time points: A = baseline sample; B = completion of proximal anastomosis; C = completion of distal anastomosis; D = 5 min post reperfusion; E = 30 min post reperfusion. Values are presented as medians with interquartile ranges.

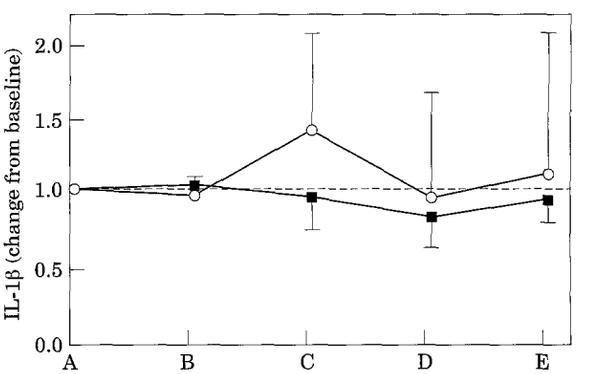

Fig. 2. Graph illustrating the changes in IL-1β generation during endovascular (■) and conventional aneurysm (○) repair. Time points: A = baseline sample; B = completion of proximal anastomosis; C = completion of distal anastomosis; D = 5 min post reperfusion; E = 30 min post reperfusion. Values are presented as medians with interquartile ranges.

($F_{ob} = 4.54$, $F_c = 4.03$: and $F_{ob} = 8.62$, $F_c = 4.03$ respectively), whereas the fall in oxygen free radicals did not reach statistical significance (Fob = 0.88, Fc = 4.03). Interleukin-6 generation did not appear to vary with conventional or endovascular repair (F_{ob} = 0.69, $F_c = 4.03$).

Discussion

Periods of tissue ischaemia followed by reperfusion, initiate a cascade of interrelated biochemical reactions which result in local and systemic organ dysfunction. During ischaemia, oxygen free radicals are generated in the cellular cytoplasm, but their injurious properties

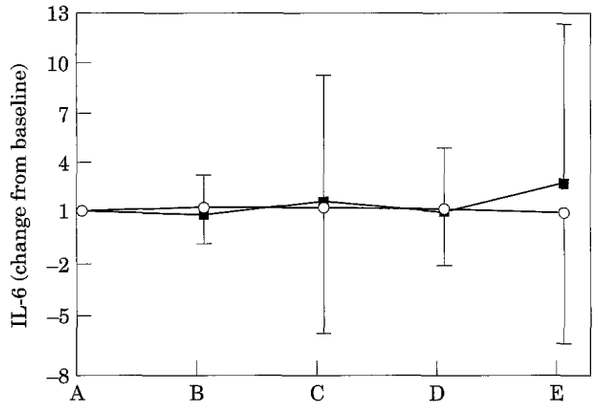

Fig. 3. Graph illustrating the changes in IL-6 generation during endovascular (■) and conventional aneurysm (○) repair. Time points: A = baseline sample; B = completion of proximal anastomosis; C = completion of distal anastomosis; D = 5 min post reperfusion; E = 30 min post reperfusion. Values are presented as medians with interquartile ranges.

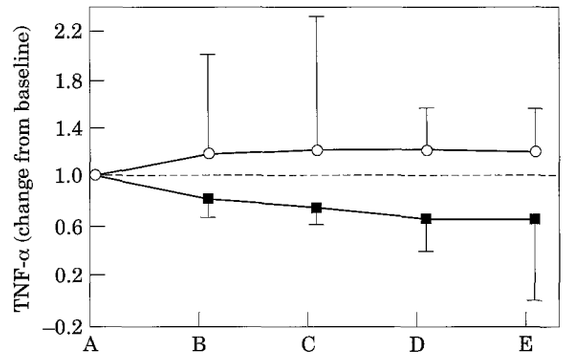

Fig. 4. Graph illustrating the changes in TNF-α generation during endovascular (■) and conventional aneurysm (○) repair. Time points: A = baseline sample; B = completion of proximal anastomosis; C = completion of distal anastomosis; D = 5 min post reperfusion; E = 30 min post reperfusion. Values are presented as medians with interquartile ranges.

are largely negated by an array of antioxidant defences.[24] Ischaemia also initiates the conversion of xanthine dehydrogenase to xanthine oxidase, with the subsequent build up of intracellular hypoxanthine. On reperfusion, xanthine oxidase catalyses the formation of uric acid from hypoxanthine with the formation of reactive oxygen species.[25] The resulting oxidant flux may exceed the cellular defence capabilities and local tissue damage will occur,[26] prinicpally due to peroxidation of polyunsaturated fatty acids in the cell membrane.[27]

Circulating neutrophils also play a pivotal role in the ischaemia - reperfusion process. During ischaemia, neutrophils become activated and bind to the microvascular endothelium, where they exert a cytotoxic action through release of proteolytic enzymes and NAPDH oxidase mediated generation of further oxygen free radicals.[28] Cytokines (e.g. IL-1β and TNF-α) and arachidonic acid metabolites are released by damaged endothelium and activated white cells, which propagate the ischaemia - reperfusion injury by enhancing both local and remote neutrophil adhesion.[29,30]

Conventional surgery for infra-renal aortic aneurysms causes an ischaemia - reperfusion insult to all structures supplied by the inferior mesenteric, iliac or femoral arteries.[31] Murphy *et al.*,[8] measured anti-oxidant compounds (α-tocopherol [Vit E], ascorbic acid and protein thiols), oxidation products (α-tocopheryl quinione), and lipid peroxidation products (lipid-derived malondialdehyde) in 24 patients undergoing thoracoabdominal aneurysm repair. During ischaemia, anti-oxidant compounds decreased, whereas α-tocopheryl quinione doubled. On reperfusion, the anti-oxidant activity remained low whilst lipid peroxidation products increased significantly. This data suggested that an oxidative stress occurred during aortic clamping, and also upon subsequent reperfusion. These observations were confirmed by Ward *et al.*[32] who demonstrated an indirect increase in oxygen free radical generation during AAA surgery. Reactive oxygen species were produced at a low rate during aortic clamping, but increased dramatically during restoration of blood flow.

Local damage to the limbs following aortic reconstruction has been reported by Formigli *et al.*[33] who showed that ultrastructural damage to lower limb musculature was initiated during aortic cross-clamping but became more severe during reperfusion. The muscular damage was associated with an infiltrate of white cells. In addition to local tissue degradation, reperfusion following aneurysm repair may be responsible for systemic organ failure. Patterson *et al.*[34,35] demonstrated that declamping of the aorta was

associated with an increase in pulmonary capillary permeability, which was attenuated by a free radical scavenger. The mechanism of injury was postulated[36] to be remote activation of circulating neutrophils, which are capable of producing mediators that increase endothelial permeability.[37]

Experimentally, ischaemia - reperfusion injury is associated with high levels of IL-1β and TNF-α[38] which are released from macrophages in response to hypoxia.[39] Roumen *et al.*[5] quantified an increase in IL-1β, IL-6 and TNF-α during AAA repair, and implied that there was a correlation between high cytokine levels and the development of adult respiratory distress syndrome and multiple organ failure, a suggestion that has been supported by others.[40,41] This study also revealed that there was a differential cytokine profile in patients subjected to ischaemia or trauma, which verified that the IL-6 response was governed mainly by the extent of tissue trauma rather than the degree of ischaemia.[42] The origin of elevated cytokine levels following aortic surgery has not been completely elucidated but it appears that reperfusion injury of the gastrointestinal tract and subsequent endotoxaemia plays a significant role.[6,43]

This study quantified cytokine and free radical generation from the lower limbs, throughout conventional and endovascular aneurysm repair. Conventional aneurysm resection was associated with measurable increases in reactive oxygen species, IL-1β and TNF-α, which confirms the findings of other investigators.[5] The concentration of interleukin-6 did not increase over the perioperative period. This may be explained as the portal circulation is the major source of IL-6 following aortic surgery,[43] and IL-6 tends to peak 1–2 h after TNF-α.[44]

Endovascular aneurysm repair utilises self-expanding or balloon expandable metallic stents to anchor an intraluminal prosthesis within an aneurysm sac. This technique allows aneurysm repair without the necessity for aortic cross clamping, although the endograft deployed in this trial required four separate balloon inflations, which occluded the aorta for 4 min in total. A reduction in the duration of total aortic occlusion has been postulated as a major advantage of endovascular repair.[45]

The main findings of this study demonstrated that endovascular aneurysm repair was associated with a marked reduction in the production of oxygen free radicals, IL-1β and TNF-α when compared to conventional surgical procedures. This suggests that the absence of conventional aortic cross clamping, decreases the extent of ischaemia - reperfusion injury. It may be hypothesised that minimising the severity of reperfusion damage may have the potential to decrease the incidence of remote organ failure following aneurysm repair, although multi-centre trials will be required to address this point. The initial data from this trial support the continued investigation of endovascular aneurysm repair and confirm the theoretical impression that a reduction in aortic occlusion may be associated with advantageous systemic effects.

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