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Review Article

Cytokines as biomarkers of inflammatory response after open versus endovascular repair of abdominal aortic aneurysms: a systematic review

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Abstract

The repair of an abdominal aortic aneurysm (AAA) is a high-risk surgical procedure related to hormonal and metabolic stress-related response with an ensuing activation of the inflammatory cascade. In contrast to open repair (OR), endovascular aortic aneurysm repair (EVAR) seems to decrease the postoperative stress by offering less extensive incisions, dissection, and tissue manipulation. However, these beneficial effects may be offset by the release of cytokines and arachidonic acid metabolites during intra-luminal manipulation of the thrombus using catheters in endovascular repair, resulting in systemic inflammatory response (SIR), which is clinically called post-implantation syndrome. In this systematic review we compared OR with EVAR in terms of the post-interventional inflammatory response resulting from alterations in the circulating cytokine levels. We sought to summarize all the latest evidence regarding post-implantation syndrome after EVAR. We searched Medline (PubMed), ClinicalTrials.gov and the Cochrane library for clinical studies reporting on the release of cytokines as part of the inflammatory response after both open/conventional and endovascular repair of the AAA. We identified 17 studies examining the cytokine levels after OR versus EVAR. OR seemed to be associated with a greater SIR than EVAR, as evidenced by the increased cytokine levels, particularly IL-6 and IL-8, whereas IL-1β, IL-10 and TNF-α showed conflicting results or no difference between the two groups. Polyester endografts appear to be positively correlated with the incidence of post-implantation syndrome after EVAR. Future large prospective studies are warranted to delineate the underlying mechanisms of the cytokine interaction in the post-surgical inflammatory response setting.

Keywords: abdominal aortic aneurysms (AAA); open repair (OR); endovascular repair (EVAR); surgical stress; cytokines

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Introduction

The repair of an abdominal aortic aneurysm (AAA) is a high-risk surgical procedure related to hormonal and metabolic stress-related responses, with an ensuing activation of the inflammatory cascade[1]. A systemic inflammatory response (SIR) is caused by both the surgical trauma and ischemia-reperfusion injury[2] related to aortic clamping[3-6] and by local cellular interactions arising at the blood/biomaterial interface[7, 8].

In contrast to open repair (OR), endovascular aortic aneurysm repair (EVAR) seems to decrease the postoperative stress by offering less extensive incisions, dissections, and tissue manipulation. However, these beneficial effects may be offset by the release of cytokines and arachidonic acid metabolites due to the intra-luminal manipulation of the thrombus by catheters during the endovascular repair, resulting in SIRS and its manifestation after endograft placement and interaction with the aortic endothelium, which is clinically called post-implantation syndrome[9]. The inflammatory response is important for tissue repair and has a profound effect on homeostasis due to release of catabolic stress hormones and the interference with immune function, which delays wound healing and increases the risk of sepsis[10, 11]. Recently, post-operative IL-6 and CRP levels were reported to correlate with the magnitude of operative injury and the invasiveness of the

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operative procedure[11].

Contributors to the surgical stress after open repair include laparotomy and ischemia-reperfusion injury after aortic cross-clamping[12]. During OR, the aorta may be approached either transabdominally or through the retroperitoneal space. Depending on the anatomy, the aorta can be reconstructed with a tube graft, an aortic iliac bifurcation graft, or an aorto-femoral bypass. For proximal infrarenal control, the first step is to identify the left renal vein. If significant intraluminal debris, juxtarenal thrombus, or prior peripheral embolization is present, the distal arteries are clamped first, followed by aortic clamping[9].

With respect to pelvic outflow, the inferior mesenteric artery is sacrificed in most instances[12]. Therefore, to prevent colon ischemia, every attempt must be made to restore the perfusion from at least one hypogastric (internal iliac) artery. If the hypogastric arteries are sacrificed (*eg*, because of associated aneurysms), the inferior mesenteric artery should be reimplanted. The aorta is reconstructed from within by using a polytetrafluoroethylene (PTFE) or Dacron graft. The aneurysm sac is closed, and the graft is placed into the duodenum to prevent erosion. Before the restoration of the lower-extremity blood flow, both forward flow (aortic) and backflow (iliac) are allowed to remove debris. The graft is also irrigated to flush out the debris[12].

Endovascular repair of an AAA involves gaining access to the lumen of the abdominal aorta, usually via small incisions over the femoral vessels[13]. An endograft, typically a polyester or Gore-Tex graft with a stent exoskeleton, is placed within the lumen of the AAA, extending distally into the iliac arteries. The graft serves to contain aortic flow and decrease the pressure on the aortic wall, leading to a reduction in the AAA size over time and a decrease in the risk of aortic rupture[14].

The aim of this systematic review was to compare OR and EVAR in terms of the post-interventional inflammatory response as yielded by the alterations in the circulating cytokine levels. Ultimately, we sought to summarize all the latest evidence regarding post-implantation syndrome after EVAR.

Materials and methods

Search strategy, data sources and eligibility criteria

This systematic review followed the guidelines proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Table S1) [15]. A predetermined study protocol was agreed upon and was strictly followed by all the authors. The identification of the eligible studies was performed using three distinct databases through November 2nd, 2017; Medline (PubMed), ClinicalTrials.gov and the Cochrane library. The following algorithm was applied: "((surgical stress) OR cytokines OR interleukin OR (systemic inflammatory response)) AND (abdominal aortic aneurysm) AND ((open OR endovascular OR conventional) AND (repair OR surgery))". Two independent reviewers (Diamantis I TSILIMIGRAS, Demetrios MORIS) screened all the articles yielded by the aforementioned algorithm. The reference lists of the eligible studies were manually assessed in order to detect any potential relevant article ("snowball" procedure).

Inclusion and exclusion criteria

Only clinical studies reporting on the cytokines released as part of the inflammatory response after both open/conventional and endovascular repair of the AAA were considered eligible. No study sample size restriction was applied. The exclusion criteria were as follows: 1) studies reporting on the repair of aneurysms other than abdominal, 2) studies reporting on either open or endovascular alone AAA repair without comparing the two approaches, 3) non-English studies, 4) animal studies, 5) reviews, 6) editorials and letters to the editors and 7) overlapping studies.

Data extraction and tabulation

Two independent authors (Diamantis I TSILIMIGRAS, Demetrios MORIS) reviewed the full-texts of the eligible studies, extracted the data and cross-checked all the results. In particular, the variables extracted included the general study characteristics (*eg*, author, year of publication, study design, number of patients pertaining to the OR and EVAR groups), the patient demographics (*eg*, age and gender), and cytokine alterations. In the case of data discrepancies, the authors reached a consensus by discussion.

Results and discussion

Search results and study characteristics

The initial search algorithm yielded 412 records. Following the screening of the titles and abstracts, 78 clinical studies were retrieved for the full-text evaluation. Fifteen studies were deemed eligible, while two were identified from the "snowball" procedure, resulting in a total of 17 studies examining the cytokine levels after OR versus EVAR[16-32] (Figure 1). All the studies were prospective, incorporating a total of 530 patients with 245 (46.2%) patients undergoing OR and 285 (53.8%) undergoing EVAR. Various cytokines were examined as biomarkers of the post-interventional inflammatory response, including IL-1β, IL-2, IL-6, IL-8 and TNF-α. However, the vast majority of the available studies (14 out of 17) focused on the role of IL-6[16-25, 27, 29, 31, 32] followed by TNF-α (7 out of 17)[10, 19, 21, 22, 25, 29, 31, 32]. The demographics of the eligible studies along with the cytokines under investigation are listed in Table 1.

Operation causes the activation of inflammatory cascade

It has long been recognized that injury to the body, either from trauma or from operative procedures causes a stereotypical cascade of neuroendocrine, cytokine, acute phase and metabolic responses[33]. Within minutes after uncomplicated elective operative injury, activation of the sympathetic nervous system occurs, resulting in increased secretion of catecholamines (epinephrine and norepinephrine) into the circulation, which leads to tachycardia, hypertension, fever and tachypnea[1]. At the same time, there is also an increased secretion of the pituitary hormones, such as corticotrophin (ACTH),

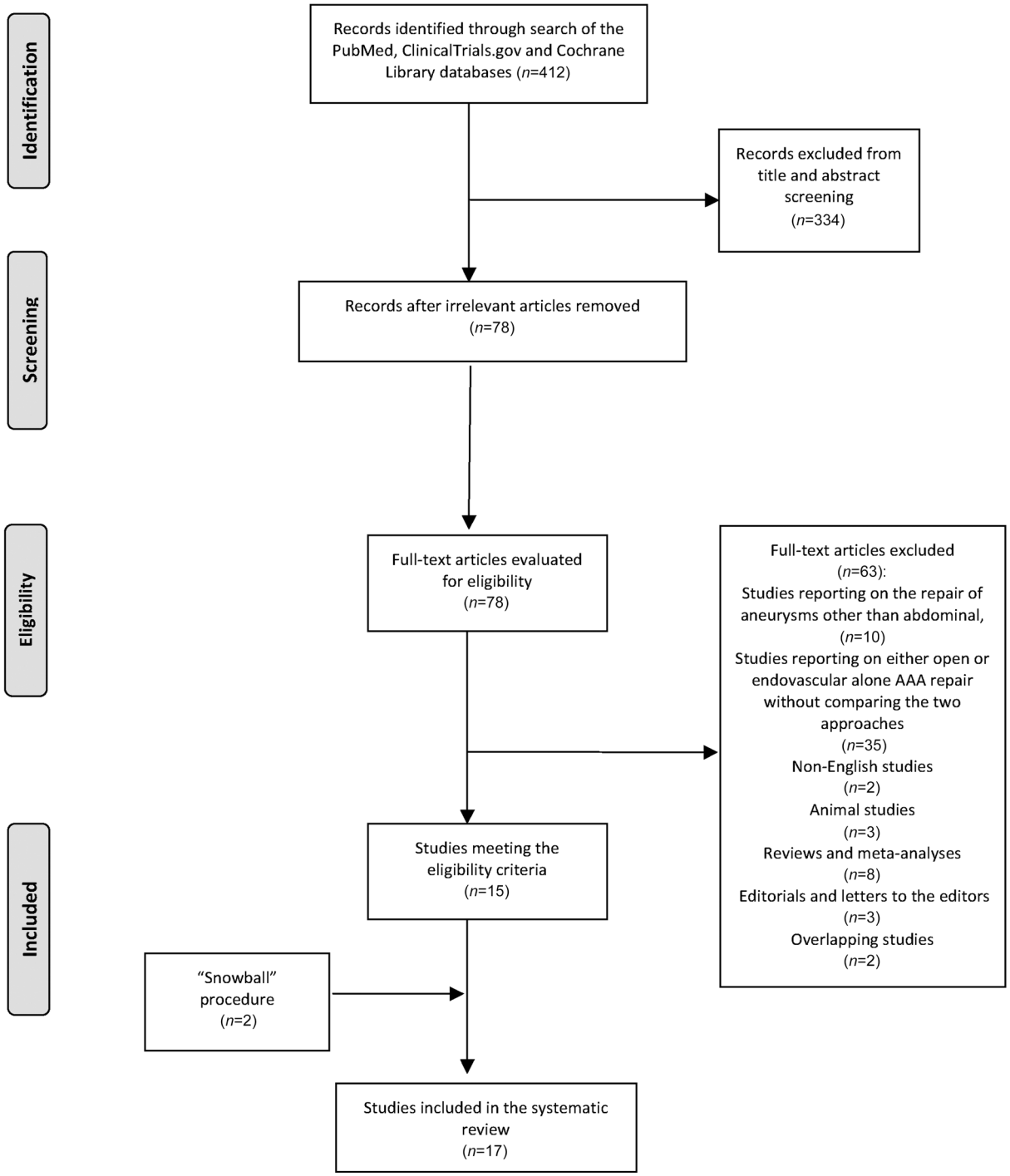

Figure 1. Flowchart of the search strategy.

growth hormone (GH) and arginine vasopressin (AVP). ACTH acts on the adrenal cortex to stimulate cortisol secretion, peaking at approximately 4–6 h after the operative injury, whereas AVP affects the kidney and fluid balance[1].

Subsequently, there is an increase in the production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1 beta, IL-8, IL-12, IL-18, and in particular, IL-6[34]. It has been suggested that IL-6 peaks at approximately 18–24 h after operative injury. These cytokines are produced in response to injury by many cells throughout the body and form a complex signaling system for the subsequent production of acute phase proteins from the liver and increase the stimulation of myeloid tissue[35-37]. Changes in circulating myeloid cells occur, particularly by increasing white blood cells (WBC), which are dominated by neutrophils as well as the increased numbers of myeloid-derived suppres-

Table 1. Demographics of the eligible studies along with the cytokines under investigation.

Authors (Year)	Study design	Total patient number	Patient number		Age		Gender		Cytokines					
			OR	EVAR	OR	EVAR	OR M/F	EVAR M/F	IL1-β	IL-2	IL-6	IL-8	IL-10	TNF-α
Makar (2013)	PS	30	16	14	71.4 ± 7.0	72.2 ± 6.2	14/2	12/2	-	-	+	-	-	-
Barry (2009)	PS	22	9	13	68 ± 2.8	68 ± 2.4	8/1	12/1	-	-	+	-	-	-
Dawson (2009)	PS	100	34	66	73.4 ± 1	74 ± 0.8	30/4	60/6	-	-	+	-	-	-
Aho (2007)	PS	32	15	17	72 ± 5	74 ± 7	12/3	15/2	+	-	+	-	+	-
Shindo (2005)	PS	32	15	17	NR	NR	NR	NR	-	-	-	+	-	-
Sweeney (2002)	PS	20	12	8	73 (68–79)	71 (71–72)	7/5	3/5	-	+	-	-	+	-
Parodi (2001)	PS	24	10	14	67 (54–85)	67 (57–79)	10/0	11/3	-	-	-	+	-	-
Bolke (2001)	PS	40	20	20	71 ± 5	72.8 ± 8.6	NR	NR	-	-	+	-	-	-
Rowlands (2001)	PS	32	16	16	74.5 (62–82)	76 (60–87)	11/5	14/2	-	-	+	+	+	-
Boyle (2000)	PS	43	20	23	67 (58–81)	72 (60–81)	18/2	23/0	+	-	+	-	-	+
Elmarasy (2000)	PS	20	10	10	67.6 ± 2.5	70.3 ± 2.6	9/1	10/0	-	-	+	-	-	+
Galle (2000)	PS	12	5	7	66.2 (1.83)*	73 (2.33)*	5/0	7/0	-	-	+	+	-	+
Morikage (2000)	PS	40	26	14	71 (35–86)	72 (63–79)	NR	NR	-	-	+	+	-	-
Odegard (2000)	PS	20	10	10	69 (64–76)	73 (68–77)	7/3	8/2	-	-	+	-	-	+
Syk (1998)	PS	37	14	23	71 (59–81)	71 (55–84)	12/2	22/1	-	-	+	-	-	+
Swartbol (1996)	PS	14	7	7	74 (69–80)	63 (52–72)	7/0	7/0	+	-	+	+	-	+
Thompson (1996)	PS	12	6	6	71 (64–85)	72.5 (64–76)	3/3	6/0	+	-	+	-	-	+
Total		530	245 (46.2)	285 (53.8)			153/31	210/24						

Continuous variables are expressed as mean±standard deviation or median (range), unless otherwise indicated.

* mean (SEM).

PS=prospective study, OR=open repair, EVAR=endovascular aortic aneurysm repair, NR=not reported; M/F=male/female; IL=interleukin; TNF-α=tumor necrosis factor-α.

sor cells and platelets. In addition, there seem to be changes in the plasma concentrations of a number of acute phase proteins, particularly C-reactive protein (CRP)[38], which peaks at approximately 48–72 h[39].

Basic principles about open and endovascular repair of AAA

For many years, OR was the mainstay of treatment for the management of AAA. Due to the significant related risk of morbidity and death[40], EVAR was introduced in 1991[41] as a less invasive procedure of transfemoral AAA management. Apart from the advantages over OR in terms of the reduced mortality and morbidity rates[42], EVAR is also associated with restricted perioperative hemodynamic parameter fluctuations[43, 44].

Differences in the postoperative stress response between EVAR and OR have been demonstrated in many studies with different underlying mechanisms pertaining to each approach[27, 45]. In general, it is thought that EVAR is associated with a less intense and extensive inflammatory response and cytokine release[32, 46], less tissue damage, ischemia-reperfusion insult and subsequent inflammatory events. On the other hand, it has also been mentioned that endoluminal procedures

may elicit an unexpected systemic inflammatory response[29, 47], which is also called post-implantation syndrome (PIS).

The length of the operation has long been recognized as predictive of the increased activation of the stress response, irrespective of the anesthetic method. Operations lasting more than 5 h are characterized by significantly higher CRP, IL-1β, IL-6, and TNF-α levels (P<0.05) at 12 and 24 h postoperatively than those lasting less than 4 h[48], which is normally the case in AAA repair. Thus, post-surgical stress may be ameliorated with minimally invasive procedures, such as EVAR. Clarifying the pathophysiology behind the aortic aneurysm repair-related surgical stress facilitates the establishment and the application of Stress Scales that could predict the postoperative course after an AAA repair in terms of the morbidity, mortality and length of hospital stay[12]. Table 2 summarizes the differential release of cytokines in the AAA repair-induced surgical stress based on the treatment approach (OR versus EVAR).

Interleukin-8 (IL-8)

IL-8 is a pro-inflammatory cytokine that plays a definite role in the regulation of neutrophil recruitment and migration[49]. IL-8 has a lower peak than IL-6 at 2–4 h after clamp removal during thoracoabdominal AAA repair[50, 51]. Parodi *et al*[26] found that IL-8 levels increased immediately after OR and fell by 72 h, although not to preoperative levels. IL-8 levels were higher in the OR group than the EVAR group even on the 7th postoperative day (P=0.02)[28]. Rowland *et al* found that IL-8 levels peaked earlier than those of IL-6 (at 4 h after clamp removal), showing a faster decline in the EVAR group (at 72 h after clamp removal: OR=35 pg/mL and EVAR: 16 pg/mL, P=0.001)[27]. Interestingly, however, older studies showed no difference between the two groups in terms of the IL-8 levels[22, 24, 29].

Interleukin-10 (IL-10)

IL-10 acts as an anti-inflammatory as well as a coagulation inhibitory cytokine, which counterbalances or regulates the pro-inflammatory response[52]. IL-10 exhibits pluripotent anti-inflammatory properties by both inhibiting TNF-α and IL-1 synthesis and antagonizing their actions through the up-regulation of cytokine antagonists[53]. In cases of major traumatic injury, an increased IL-10 production, in combination with decreased IFN-γ and IL-12, correlates with cellular immunity suppression[54]. Thus, the systemic release of IL-10, triggered by sympathetic nervous system activation, might be a key mechanism of the immunosuppression observed after injury, which predisposes patients to the development of infections[55].

Given that AAA repair provokes a major tissue trauma, these interactions may explain the mechanism of wound infection. It has been shown that IL-10 levels peak during the ischemic phase in aneurysm surgical repair, while returning to baseline during visceral perfusion[56] and, therefore, presents with a biphasic pattern[57]. Among the studies examining the differences in the cytokine release between OR and EVAR, none found significant differences between the two approaches[16, 27, 30]. IL-10 levels were comparable at 0 h, 4 h, 24 h, 72 h and 144 h after clamp removal[27]. Interestingly, after elective AAA repair, high levels of IL-10 were associated with both prolonged critical care (P<0.001) and hospital stay (P=0.001)[58].

Interleukin-6 (IL-6)

Among all the cytokines, IL-6 has been at the forefront of the studies examining the postoperative inflammatory response after OR or EVAR[16-25, 27, 29, 31, 32] (Table 2). IL-6 release follows the same pattern as other acute phase cytokines (TNF-α, IL-1 and IL-10) and peaks between 4 and 48 h after clamp removal[31]. However, it demonstrates the most pronounced increase and thus is supposed to reflect the intensity of the surgical trauma following AAA repair[2, 58]. Several clinical studies have suggested that the major source of IL-6 following AAA repair may be the splanchnic system rather than the lower limb[59]. It has been hypothesized that IL-6 uptake through the liver may be preserved in cases of sufficient visceral organ protection[56, 60]. Thus, a persistent rise in IL-6 levels in the postoperative period may be a valuable predictor of serious complications[3, 61].

Most reports (8 out of 14 eligible studies) have advocated the higher IL-6 release following OR when compared to the EVAR approach[16, 18, 19, 21, 25, 27, 29, 31]. It has been suggested that the production of IL-6 in OR should be attributed to tissue damage (caused by ischemia-reperfusion injury and surgical insult) or blood transfusion, whereas IL-6 release in EVAR may be caused by manipulations into the aneurysmal thrombus[22]. IL-6 levels peak between 4 and 48 h postoperatively with OR, inducing a higher IL-6 response[16, 18, 19, 21, 25, 29, 31], and IL-6 is present even on the 6th postoperative day (POD)[27].

In contrast, Galle *et al* revealed similar IL-6 release patterns between the OR and EVAR, demonstrating the involvement of IL-6 in the inflammation process in both procedures[22]. The same results were obtained by two other studies at 5 min, 60 min, 24 h and 48 h postoperatively[17, 32], whereas Dawson *et al* and Morikage *et al* revealed lower concentrations of circulating IL-6 with OR compared to EVAR (P=0.03) and unrepaired AAA (P=0.025)[20, 24].

Recently, Makar *et al*[23] investigated the SIRS following EVAR and OR in the ruptured AAA setting. They found that IL-6 decreased in both groups after surgery, reaching parity on the POD5[23]. The peak IL-6 was significantly higher in the OR group (25.1 (17.2–50.9 pg/mL)) than in the EVAR group (14.2 (7.1–29.8 pg/mL; P=0.04))[23]. However, the IL-6 levels were similar at the individual time points (6 h, POD1, POD3, POD5) in both groups. Interestingly, previous studies have associated the high IL-6 levels with the development of multi-organ failure in cases of AAA rupture (P=0.01)[58, 62]. In a recent systematic review by Watt *et al*, OR presented a peak value of IL-6 at the level of 332 pg/mL compared to the 116 pg/mL seen in EVAR[11].

Interleukin-1β and TNF-α

Calogero *et al*[63] demonstrated that IL-l concentrations increase

Table 2. Differences in cytokine levels after OR versus EVAR as markers of inflammatory response.

Author	Year	Cytokines	Findings
Makar *et al*.	2013	IL-6	*Ruptured AAA. The peak IL-6 was significantly higher in the eOR group (25.1 (17.2–50.9 pg/mL)) compared to the eEVAR group (14.2 (7.1–29.8 pg/mL; *P*=0.04)). However, IL-6 levels were similar at the individual time points (6 h, POD1, POD3, POD5) in both groups.
Barry *et al*.	2009	IL-6	No statistically significant difference was seen between EVAR and OR at 5 min, 60 min, 24 h and 48 h postoperatively (although largest difference was noted at 24 h post operatively; OR: 178.2±49 pg/mL *vs* EVAR: 98.88±28.8 pg/mL, *P*>0.05).
Dawson *et al*.	2009	IL-6	OR was associated with significantly lower concentrations of circulating IL-6 compared to EVAR (*P*=0.03) and unrepaired AAA (*P*=0.025). There was no significant difference in IL-6 between the unrepaired and EVAR groups (*P*=0.66).
Aho *et al*.	2007	IL-1β	No differences between OR and EVAR
		IL-10	No differences between OR and EVAR
		IL-6	Higher level of IL-6 in OR versus EVAR group on POD1, but not POD3, POD7.
Shindo *et al*.	2005	IL-8	In OR IL-8 levels were higher than the EVAR even on the POD7.
Sweeney *et al*.	2002	IL-2	Higher IL-2 levels in OR versus EVAR only on the POD7 (*P*=0.048), not POD1
		IL-10	No changes in IL-10 at any time point in either group.
Bolke *et al*.	2001	IL-6	Significantly higher peak IL-6 levels in the OR versus EVAR group (*P*<0.05).
Rowlands *et al*.	2001	IL-6	Higher IL-6 levels in OR versus EVAR group at 4 h, 24 h, 72 h and 144 h after clamp removal.
		IL-8	IL-8 peaked earlier than IL-6 (at 4 h) in both groups. Faster decline in EVAR versus OR (at 72 h after clamp removal: OR=35 pg/mL and EVAR: 16 pg/mL, *P*=0.001).
		IL-10	No significant differences between OR and EVAR groups at 0 h, 4 h, 24 h, 72 h and 144 h after clamp removal.
Parodi *et al*.	2001	IL-8	IL-8 levels increased immediately after OR and fell by 72 h, although not to preoperative levels. Higher IL-8 levels in the OR versus EVAR on POD1.
Boyle *et al*.	2000	IL-1β	No significant difference was found in the IL-1β results between the groups.
		IL-6	EVAR: IL-6 levels were significantly lower in this group on POD1 (median 120 versus 277 pg/mL; 99% CI=51 to 243, *P*=0.0038) and POD2 (43 versus 256 pg/mL; 99% CI=71 to 266, *P*=0.0002).
		TNF-α	EVAR: lower TNF-α levels 30 min after reperfusion (11.1 versus 22.5 pg/mL; 99% CI=4.8 to 20.8, *P*=0.0074); 6 h after surgery (11.0 versus 27.5 pg/mL; 99% CI=7.2 to 1.5, *P*=0.0004); POD 1 (9.8 versus 16.6 pg/mL; 99% CI=2.4 to 14.5, *P*=0.007); and POD3 (10.2 versus 23.6 pg/mL; 99% CI=7.8 to 19.0, *P*=0.0043).
Elmarasy *et al*.	2000	IL-6	Higher IL-6 levels in the OR versus EVAR group from the 2 h to the 24 h post-reperfusion.
		TNF-α	Higher TNF-α levels in the OR versus EVAR group at 4 h, 6 h, 8 h and 12 h post-reperfusion. From the 16 h onwards, no differences were seen.
Galle *et al*.	2000	IL-6	IL-6 revealed significantly higher response in the EVAR and OR groups than in the controllers, with IL-6 release patterns being similar in the EVAR and OR groups.
		IL-8	No significant differences between the two groups.
		TNF-α	No statistically significant tendency toward early acute TNF-α production in EVAR and no TNF-α production in OR.
Morikage *et al*.	2000	IL-6	EVAR: higher IL-6 levels on POD 1, 3 and 6; however, statistical significance was reached only on POD1.
		IL-8	No differences between the two groups throughout the study period.
Odegard *et al*.	2000	IL-6	IL-6 higher release after OR when compared with those of EVAR group.
		TNF-α	No significant changes in TNF-α after treatment.
Syk *et al*.	1998	IL-6	IL-6 peaks between 4 and 48 h postoperatively (after reperfusion) with higher values in the OR than the EVAR group.
		TNF-α	More pronounced TNF-α release in OR versus EVAR group.
Swartbol *et al*.	1996	IL-1β	Only modest elevation with no significant differences between the groups. IL-1β demonstrated the maximum at 60 min post-clamp.
		IL-6	IL-6 levels were significantly higher in OR patients (*P*<0.0005).
		IL-8	IL-8 was not detected in any patient.
		TNF-α	TNF-α release was recorded in the EVAR group only.
Thompson *et al*.	1996	IL-1β	Lesser increase in IL-1β and TNF-α from baseline with EVAR compared to OR.
		TNF-α	
		IL-6	IL-6 did not vary between EVAR and OR.

AAA=abdominal aortic aneurysm; IL=interleukin; TNF-α=tumor necrosis factor-α; OR=open repair; EVAR=endovascular aortic aneurysm repair; POD=postoperative day; PS=prospective study; CI=confidence interval; h=hour.

mainly during periods of major surgical manipulation with a second surge at the emergence from general anesthesia and during the postoperative recovery period. Only 4 studies examined the differential release of IL-1β in the OR versus EVAR group[16, 19, 29, 32]. It has been largely suggested that IL-1β levels exhibit no differences between the two groups[16, 19, 29], with the highest intraoperative IL-1β levels recorded 60 min after clamp removal[29]. Only Thompson *et al* found a lower increase in IL-1β and TNF-α levels from baseline with EVAR compared to OR[32].

TNF-α enhances vascular permeability through both neutrophil-dependent and neutrophil-independent mechanisms[64], and high TNF-α levels have been correlated with poor outcomes after OR[3, 61, 65]. Some studies revealed a more pronounced TNF-α release in OR versus EVAR[19, 21, 31, 32]. In contrast, two other studies[22, 25] reported no significant changes in TNF-α after EVAR or OR. Of note, Swartbol *et al* described TNF-α release only in the EVAR group[29]. Other observations about EVAR[19, 29, 47] described a TNF-α response associated with a clinically relevant drop in blood pressure or as a consequence of leukocyte activation triggered by IL-6 release from the aneurysmal thrombus during manipulations[66]. These findings indicate that surgical stress alone does not normally produce TNF-α. Hemorrhage or shock, such as in case of a ruptured AAA, are related to significant increases in TNF-α, whereas only modest elevations if none are detected following uncomplicated elective AAA repair[2, 51, 67]. High TNF-α levels are also correlated with renal or other organ dysfunction[3, 58, 68] and a higher mortality (P=0.01)[57, 69].

The role of the material in the postimplantation syndrome

Patients undergoing EVAR for AAA often develop an inflammatory response, called postimplantation syndrome (PIS), that is associated with fever and leukocytosis[70]. The reported incidence of PIS in the literature varies widely from 14% to 60%[13, 71]. PIS constitutes a SIRS state, as it actually fulfills at least two of the SIRS criteria (fever and leukocytosis)[72]. However, hs-CRP values have also been strongly related to the presence of PIS and emerged as an important predictor of the 30-day outcome[9].

The endograft type appears to influence the incidence of SIR after EVAR. PIS is mainly apparent during the first 24 h and decreases afterward. Anaconda and Zenith endografts are thought to induce a more intense inflammatory response. A "milder" inflammatory activation was observed in patients with an Excluder endograft[14]. PIS is not associated with perioperative adverse clinical events, showing a benign course. Moulakakis *et al*[14] compared the variability of PIS throughout different the endograft types and concluded that the mean elevated temperature was more pronounced postoperatively in the Anaconda group, whereas all the grafts caused a significant increase in the serum levels of IL-6 and IL-10 postoperatively compared with the preoperative levels. The Excluder group showed the smallest increase in the levels of serum IL-6 and IL-10 at 24 h and 48 h, postoperatively[14]. The mean differences in the cytokine levels after aneurysm exclusion were greater for the Anaconda versus the Excluder group (P<0.01) than for the Anaconda versus Zenith group (P<0.05). No differences in the mortality and morbidity rates were observed among the four groups[14]. Another study also reached the conclusion that PIS is a benign complication after EVAR using the Anaconda endograft, mainly affecting the length of the in-hospital stay and the daily physical activities of the patients with PIS[73].

Differences between the type of the stent graft deployed and the development of PIS might indicate that different materials, and maybe configurations of the grafts, interfere with the inflammatory response. Stent grafts are a collapsible hybrid product composed of either woven Dacron or ePTFE with stents providing radial support. In 2005, Gerasimidis *et al*[74], in a relatively underpowered study, found, for the first time, that fever was more common in a group of patients who received polyester endovascular grafts than in those who received the PTFE graft. IL-8 was higher in the first group, suggesting a stronger host reaction to the specific material[74]. Voûte *et al*[75], in a later study, showed that the implantation of the stent grafts based on polyester was independently associated with a stronger inflammatory response. Arnaoutoglou *et al*[9] found that the use of a polyester endograft independently predicted PIS and was correlated with a greater than 10 times higher risk for an inflammatory response. Based on the results of the 3 studies mentioned above, the type of endograft material seems to play a principle role in PIS development and may have a predictive role for a significant portion of EVAR patients. Arnaoutoglou *et al*[9] evaluated the characteristics of PIS in patients after EVAR, showing that preoperative WBC count values (P<0.001), polyester endograft material (P<0.001) and heart failure (P=0.03) were independent predictors of PIS. Postoperative hs-CRP (P=0.001) and the duration of fever (P=0.02) independently predicted the occurrence of a major cardiovascular event (MACE). A threshold of postoperative hs-CRP value of 125 mg/L was highly associated with the occurrence of a MACE, with a sensitivity of 82% and a specificity of 75%[9].

Furthermore, there are other differences between stent grafts, unrelated to graft material, which theoretically might also influence PIS occurrence. The vast majority of the stent grafts have an exoskeleton made of nitinol. Since the presentation of nitinol for medical application, it has been extensively used in coronary and peripheral arterial stents. No inflammatory response is reported in these applications, despite the frequent treatment of multiple and lengthy lesions, requiring large quantities of the material. It is, therefore, doubtful that variances in the application of nitinol between stent grafts have any effect on PIS[13].

Finally, the Nellix EndoVascular Aneurysm Sealing (EVAS) System (Endologix, Inc, Irvine, CA, USA) is a novel approach to AAA treatment, whereby a polymer is used to fill the AAA sac. A recent study demonstrated that the incidence of postimplantation syndrome (P=0.07), the mean body temperature (P=0.05), the mean leukocyte count (P=0.003), and the mean hs-CRP (P<0.001) were proportionally lower with EVAS than

with EVAR. Serious adverse events (0% *vs* 12.8%, *P*=0.05) and endoleaks (0% *vs* 10.3%, *P*=0.13) over 30 days were less frequent with EVAS, but the differences between the groups were not significant[76]. The choice of endovascular graft material influenced the postoperative and 30-day clinical outcomes, with a greater overall risk observed with the polyester stent-grafts[76].

Opinion

Major surgical procedures-such as AAA repair-often lead to severe immunosuppression, which in turn may contribute to infectious complications and sepsis. Strong stimulation of the sympathetic/adrenomedullary system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis correlates with the severity of the surgical injury and poor prognosis[77]. Corticotropin acts on the adrenal cortex to stimulate cortisol secretion, peaking at approximately 4–6 h after operative injury[77]. The simultaneous activation of these two systems allows the organism to adapt and maintain or regain homeostasis during the stress of the perioperative period. The perioperative imbalance between Th1 and Th2 cytokines has been suggested as a mechanism of the immune suppression after surgery[78]. Briefly, Th1 cytokines, such as TNF-α, IL-2 and IL-12, are highly effective at enhancing immune surveillance. By contrast, Th2 cytokines (IL-4, IL-5, IL-10, and IL-13) have a predominant immune suppressive effect[79].

IL-6 demonstrates the most pronounced increase and reflects the intensity of surgical trauma following a major operation[80]. The increase in IL-6 levels is indicative of the activation of macrophages as antigen-presenting cells in a cell-mediated inflammatory response as well as the activation of endothelial cells, which is probably due to the endograft-aortic wall interaction. It is known that the major source of IL-6 following EVAR is the aneurysmal thrombus[8]. It appears to be involved in the pathogenesis of multiple-organ failure and is a potent inducer of fibrinogen production by hepatocytes[77]. It peaks at approximately 18–24 h after operative injury, and the more extensive the operation is, the greater is the magnitude of its circulating levels[80]. TNF-α is an essential component of the host immune response to trauma and is responsible for the release of other pro- and anti-inflammatory mediators[77]. In the study by Rettig *et al*, SIRS (systematic inflammatory response syndrome) and TNF-α, as a marker of this syndrome, does not seem to be associated with an increased risk of postoperative complications[81]. This might imply that the majority of the postoperative complications are the outcome of locally induced inflammatory responses rather than systemic ones. Moreover, the authors showed no correlation between TNF-α and IL-6 in patients with postoperative complications. This is different from findings of a recent study demonstrating that TNF-α levels were positively correlated with those of IL-6 levels in patients with postoperative sepsis[82]. Finally, despite the increased IL-6 levels after major surgery and the associated increased susceptibility to postoperative infections, the serum obtained postoperatively from patients after a major operation induces an immunosuppressive response reflected by the reduced MHC class II antigens reversible by IFN-γ through IL-6-independent pathways[82]. IL-10 acts as an anti-inflammatory cytokine that counterbalances the pro-inflammatory response. In cases of traumatic major injury, an increased production of IL-10 and a decreased production of IFN-γ and IL-12 correlate with cellular immunity suppression[77]. Thus, a high production of IL-10 could counterbalance the pro-inflammatory response induced by TNF-α and IL-6 and explain the decline in SIRS and IL-6 levels during the first 5 postoperative days after a major operation. Similarly, the evaluation of INF-γ, IL-2 and IL-8 levels suggests the involvement of the Th1 pathway of cell-mediated immunity (JAK-STAT and TLR pathway).

The possibility of a systematic response to endograft has been evaluated by TNF expression[83], since it crosstalks with macrophages and causes a systematic inflammatory response, including fever, neutrophil and endothelial cell activation (TRADD-TRAF pathway). Similarly, the evaluation of INF-γ, IL-2 and CD40L levels indicate the involvement of the Th-1 pathway of cell-mediated immunity (JAK-STAT and TLR pathway) and T-dependent antibody production (CD40L). In the same frame, the expression of TGF-β acts as anti-inflammatory cytokine and indicates the counterbalance of the pro-inflammatory response of IL-6 and explains the deterioration of SIRS/PIS during the first 5 days after EVAR[84].

A high expression of markers such as CCR7 and CD62L is indicative of immune memory and would be a striking finding, since it would imply that patients with PIS have already been exposed to antigens similar to endografts (mimicry) and thus demonstrate a more robust inflammatory response.

Figure 2 illustrates the proposed pathophysiology of the inflammatory response after AAA repair. A diagrammatic presentation of the main study findings is provided in Figure 3.

Study limitations

The present review has limitations mainly due to high heterogeneity of the included studies. The PIS definition varied throughout the literature. Moreover, the study populations were not similar, and the study design was not consistent in all the studies. There are not enough comparable studies evaluating cytokines in both OR and EVAR patients. Furthermore, the current trend in US centers for patients after EVAR includes discharge at POD1, which means that it is difficult to document PIS symptoms, which present after POD2 per the definition. The value of treating SIRS/PIS is underestimated in the literature since it is considered a benign homeostatic response to surgical stress. After the publication of a prospective study demonstrating that patients with PIS after EVAR had an increased risk of a MACE during the first year, the benign character of the syndrome as well as its management should be revisited. The current literature also lacks an understanding of the pathophysiology of the PIS. This is the reason why current studies fail to answer fundamental questions regarding the cytokines involved in the pathogenesis of PIS. The expression of these cytokines does not define the syndrome. They can only describe the syndrome, elucidate

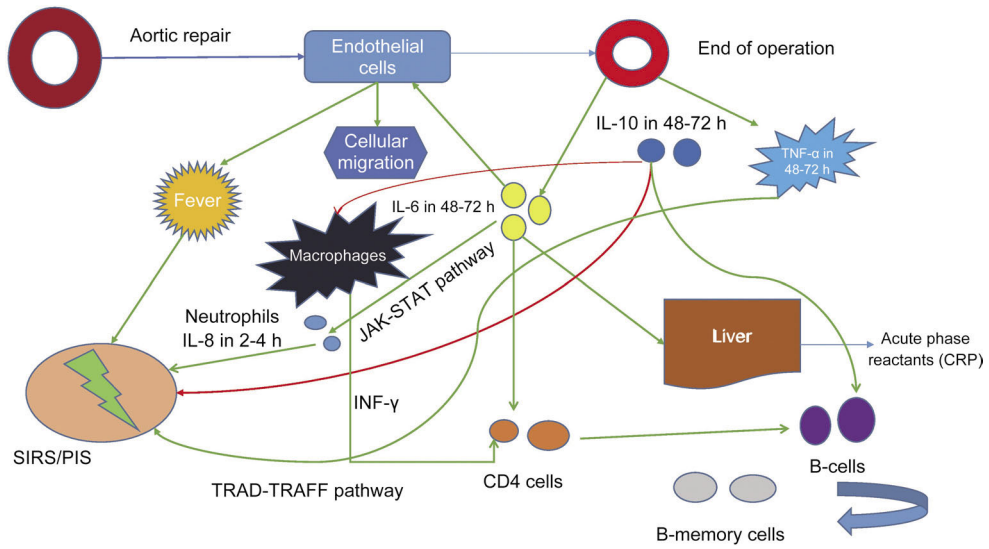

Figure 2. Proposed pathophysiology of inflammatory response after AAA repair.

Eligibility criteria

Inclusion criteria
Clinical studies reporting on the cytokines released as part of the inflammatory response after both open/conventional and endovascular repair of the AAA.

Exclusion criteria
1) studies reporting on the repair of aneurysms other than abdominal,
2) studies reporting on either open or endovascular alone AAA repair without comparing the two approaches,
3) non-English studies,
4) animal studies,
5) reviews,
6) editorials and letters to the editors and
7) overlapping studies.

Findings/Outcomes

- Open repair seems to be associated with a greater SIR compared to EVAR as reflected by the increased cytokine levels, particularly IL-6 and IL-8.
- IL-6 demonstrates the most pronounced increase and reflects the intensity of surgical trauma following a major operation. It peaks approximately 18–24 hours after operative injury. The more extensive the operation, the greater the magnitude of its circulating levels.
- Circulating IL-6 could become an excellent marker of an inflammatory reaction and act as a useful predictive biomarker of postoperative morbidity.
- IL-1β, IL-10 and TNF-a showed conflicting results or no difference between the two groups.
- Polyester endografts appear to positively correlate with the incidence of post-implantation syndrome after EVAR.

Figure 3. Diagrammatic presentation of main findings of the study.

the immune mechanisms involved and facilitate therapeutic management.

Conclusions

In conclusion, OR is associated with a greater SIR compared to EVAR, as reflected by the increased cytokine levels, particularly IL-6 and IL-8. Circulating IL-6 might be an excellent marker of an inflammatory reaction and act as a useful predictive biomarker of postoperative morbidity. We suggest that a further, more detailed analysis of the postoperative immune response will contribute to the development of more accurate and sensitive predictive biomarkers for the postoperative morbidity of AAA.

Polyester endografts are positively correlated with the incidence of post-implantation syndrome after EVAR. Future large prospective studies are warranted to delineate the underlying mechanisms of the cytokine interaction in the post-surgical inflammatory response setting.

Supplementary information

Supplementary information is available at the website of Acta Pharmacologica Sinica.

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