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Review Article

Concept of the aortic aneurysm repair-related surgical stress: a review of the literature

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Abstract: Objective: Abdominal aorta aneurysm (AAA) is a serious threat for human life. AAA repair is a high-risk procedure which results in a severe surgical stress response. We aim to give a conceptual description of the underlying pathophysiology of stress after surgical repair of AAA. Methods: The MEDLINE/PubMed database was searched for publications with the medical subject heading "surgical stress" and keywords "abdominal aortic aneurysms (AAA)", or "cytokines" or "hormones" or "open repair (OR)" or "endovascular repair (EVAR)". We restricted our search to English till 2012 and only in cases of abdominal and thoracoabdominal aneurysms (TAAA). Results: We identified 93 articles that were available in English as abstracts or/and full-text articles that were deemed appropriate for our review. Conclusions: Literature highlights no statistical significance for early acute TNF-α production in EVAR and no TNF-α production in OR. IL-6 and IL-8 levels are higher after OR especially when compared with those of EVAR. IL-10 peak was observed during ischemic phase in aneurysm surgical repair. Cortisol and epinephrine levels are higher in OR patients in comparison to EVAR patients. Finally, the incidence of systemic inflammatory response syndrome was significantly higher in OR than EVAR patients.

Keywords: Surgical stress, abdominal aortic aneurysms (AAA), cytokines, hormones, open repair (OR), endovascular repair (EVAR)

Introduction

Abdominal aortic aneurysm (AAA) is a serious threat for human life, especially when rapture is the first symptom. AAA repair is a high-risk surgical procedure which results in severe hormonal and metabolic stress-related response comprising variable endocrinologic and immunologic changes [1]. Systemic inflammatory response (SIR) is caused by both 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].

The pathophysiology of SIR involves activated neutrophils, endothelial cells, and macrophages [8] - and is mediated by a cascade of endotoxin, pro-inflammatory and anti-inflammatory cytokines [2, 9] - in addition to complement components [10] and leukotrienes [11] which facilitate the migration of activated leukocytes [3-5].

The inflammatory response is important for tissue repair and has profound effects on homeostasis due to release of catabolic stress hormones and interference with immune function, which can delay wound-healing and increase risk of sepsis [12].

Basic principles about open and endovascular repair of AAA

Open repair (OR) for AAA encompasses significant risk of morbidity and death [13]. Endovascular aneurysm repair (EVAR) was introduced early in the last 2 decades for the treatment of AAA [14] offering an apparently less invasive procedure of transfemoral EVAR management. The latter is believed to offer several advantages over OR in terms of reduced mortality and morbidity rates [15] and restricted perioperative hemodynamic parameter fluctuations [16, 17]. Differences in the inflammatory response to EVAR and OR have been demonstrated by many authors [18, 19] and the

mechanism by which the inflammatory response is generated is different. It is shown that EVAR leads to a less intense and extensive inflammatory response and cytokine release [20, 21] with less tissue damage, ischemia-reperfusion insult and subsequent inflammatory events. On the contrary, it has also been mentioned that endoluminal procedures may elicit an unexpected systemic inflammatory response [22, 23] also mentioned as postimplantation syndrome.

Methods

The MEDLINE/PubMed database was searched for publications with the medical subject heading "surgical stress" and keywords "abdominal aortic aneurysms (AAA)", or "cytokines" or "hormones" or "open repair (OR)" or "endovascular repair (EVAR)". We restricted our search to English till 2013 and only in cases of abdominal and thoracoabdominal aneurysms (TAAA). We could not evaluate the stress response from approaches such as thoracic endovascular aortic repair (TEVAR), fenestrated endovascular aneurysm repair (FEVAR) or hybrid techniques due to lack of relevant data in the literature. We sought to review the pathophysiology behind surgical stress that is attributed in surgical repair of AAA.

Results

We identified 83 articles that were available in English as abstracts or/and full-text articles that were deemed appropriate for our review.

The role of cytokines during AAA surgical repair

TNF-α, IL-6 and IL-8 as pro-inflammatory cytokines that would modulate injury [24, 25]. These cytokines have been well investigated in aneurysm surgical repair [26-29].

Interleukin 8 (IL-8)

IL-8 is one of the more potent pro-inflammatory cytokines and is generated by various cells in response to multiple stimuli. It is a member of the CXC family of chemokines and a major regulator of neutrophil recruitment and migration [30]. IL-8 seems to have a lower peak than that of IL-6 at 2-4 h after reperfusion during TAAA repair [28, 29]. Its peak is closely correlated with the degree of complement activation [27]. IL-8 levels seem to increase distinctly after skin closure in a level more pronounced than that of IL-6, which can be attributed to the fact that IL-6 production was more sufficiently suppressed than other cytokines [31]. Parodi et al. [32] measured IL-8 finding that levels increased immediately after OR and fell by 72 hours, although not to preoperative levels. In OR IL-8 levels were higher than the EVAR even in the 7th postoperative day ($p = 0.02$) [33].

Interleukin 10 (IL-10)

IL-10 acts as an anti-inflammatory as well as a coagulation inhibitory cytokine, which can counterbalance or regulate the pro-inflammatory response [25]. In cases of traumatic major injury, an increased production of IL-10 and a decreased production of IFN-γ and IL-12 correlate to cellular immunity suppression [34]. Additionally, a systemic release of IL-10 triggered by sympathetic nervous system activation might be a key mechanism of immunosuppression observed after injury that is associated with a high incidence of infection [35]. It is not abrupt to hypothesize that in cases of major surgical traumas, such as these during AAA surgical repair, this mechanism explains wound infection. During ischemic phase in aneurysm surgical repair a IL-10 peak was observed with its levels returning to baseline during visceral perfusion [31], presenting with a biphasic pattern [36]. When comparing TAAA and AAA repair, IL-10 was produced in both procedures during aortic clamping. Peak IL-10 plasma levels in TAAA repair are significantly ($p < 0.05$) higher compared to the peak IL-10 plasma levels seen during AAA repair [28, 37]. After elective AAA high levels of IL-10 were associated with both prolonged critical care ($p < 0.001$) and hospital stay ($p = 0.001$) [38]. The role of the anti-inflammatory cytokine IL-10 during surgical repair of a TAAA is recently evaluated in a Phase I study [39] presenting pluripotent anti-inflammatory properties by both inhibiting TNF-alpha and IL-1 synthesis and antagonizing their actions through up-regulation of cytokine antagonists [39].

Interleukin 6 (IL-6)

IL-6 demonstrates the most pronounced increase and reflects the intensity of surgical

trauma following AAA repair [2, 38]. It is also strongly involved in the pathogenesis of multiple-organ failure [9] and considered to be a potent inducer of fibrinogen production in the hepatocytes [38]. Its release follows that of acute phase cytokines, such as TNF-α, IL-1 and IL-10 and peaks between 4 and 48 h postoperatively (after reperfusion) with higher values in the OR than the EVAR group ($p < 0.05$) [40]. 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 [24]. In cases of rupture, the development of multi-organ failure is associated with high levels of IL-6 ($p = 0.01$) [38, 41]. In cases of TAAA repair, a substantial peak of IL-6 level was reported at 2-8 h after visceral reperfusion ($p < 0.05$) [24, 27-29, 31]. Another possible underlying mechanism may be the preserved IL-6 uptake function through the liver due to sufficient visceral organ protection [31, 42]. Many reports have described IL-6 and/or IL-8 release after OR especially when compared with those of EVAR group [3-5, 22, 23, 43-46]. For this reason, a persistent rise in IL-6 levels in the postoperative period may be a valuable predictor of serious complications [3, 43]. Some reports have shown that OR induce a higher IL-6 response [22, 40] either due to tissue damage caused by reperfusion injury or surgical trauma or that EVAR failed to induce IL-8 release [22, 40]. In another study IL-6 revealed significantly higher response in the EVAR and OR groups than in the controllers [47], with IL-6 release patterns being similar in the EVAR and OR groups demonstrating involvement of IL-6 in the inflammation process in both procedures [47]. It is 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 [47].

Tumor necrosis factor alpha (TNF-α)

TNF-α enhances vascular permeability through both neutrophil-dependent and independent mechanisms [48]. Its response after aortic surgery seems to be controversial. Although some studies showed high TNF-α levels, correlated with poor outcome after OR [3, 43, 44], others described a more pronounced TNF-α release in OR versus EVAR or failed to demonstrate release of TNF-α in any group [40]. Other observations about EVAR [22, 23, 46] 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 [49]. On the contrary, Boyle et al. [46] and Galle et al. [47] reported a not statistically significant difference in early acute TNF-α production between EVAR and OR. These findings indicate that surgical stress alone does not normally produce TNF-α. Increases in TNF-α can be clearly detected after hemorrhage or shock, such as ruptured AAA, whereas TNF-α can be detected within normal or at slightly elevated levels following uncomplicated elective AAA repair [2, 27, 29]. In TAAA repair, pronounced increases in TNF-α are observed, unless visceral or distal perfusion is used [26-28, 31]. TNF-α levels are correlated with renal or other organ dysfunction [3, 9, 38] and higher mortality ($p = 0.01$) [36, 50].

Interleukin 1α (IL-1α)

IL-1α is expressed by platelets and activated monocytes/macrophages [51]. The presence of high titers of IL-1α in the serum of patients with AAA demonstrated positive correlation with preoperative AAA size and significantly being reduced after surgery, indicating that this cytokine might be a marker of successful surgical outcome or disease progression and associated complications in longer-term follow-up [52]. Moreover, the involvement of IL-1α in endothelial cell inflammation indicates that this cytokine is involved in the molecular pathology of AAAs and thus it could have potential as a biomarker of disease behavior and/or development prior to the point of surgical intervention [52]. EVAR surgical intervention significantly decreases IL-1α [52]. Calogero et al. [53] demonstrated that IL-I concentrations increase mainly during periods of major surgical manipulation with a second surge at emergence from general anesthesia and during the postoperative recovery period. **Table 1** summarizes the role of cytokines in the AAA repair-induced surgical stress.

The role of hormones in AAA repair-induced surgical stress

Major surgical procedures, such as AAA repair often lead to severe immunosuppression,

Table 1. The role of cytokines in the AAA repair-induced surgical stress

Author	Year	Procedure	Cytokine	Findings
Welborn et al. [28]	2000	OR (TAAA)	IL-8	L-8 has lower peak than that of IL-6 at 2-4 h after reperfusion during TAAA
			IL-10	Peak IL-10 plasma levels in TAAA repair are significantly higher compared to the peak IL-10 plasma levels seen during AAA
Hanssen et al. [29]	2008		IL-8	IL-8 has lower peak than that of IL-6 at 2-4 h after reperfusion during TAAA
Kunihara et al. [31]	2011	OR (TAAA)	IL-8	IL-8 levels increased distinctly after skin closure in a level more pronounced than that of IL-6
Parodi et al. [32]	2001	Both (OR&EVAR)	IL-8	IL-8 levels increased immediately after OR and fell by 72 hours, although not to preoperative levels
Shindo et al. [33]	2005	Both	IL-8	In OR IL-8 levels were higher than the EVAR even in the 7th postoperative day
Oldenburg et al. [37]	2000	OR (TAAA vs. AAA)	IL-10	Peak IL-10 plasma levels in TAAA repair are significantly higher compared to the peak IL-10 plasma levels seen during AAA
Bown et al. [38]	2001		IL-10	After elective AAA, high levels of IL-10 were associated with both prolonged critical care and hospital stay
Syk et al. [40]	1998	Both	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	Examining both EVAR and OR described a more pronounced TNF-α release in OR
Swartbol et al. [22]	1996			
Norgren et al. [23]	1997			
Odegard et al. [45]	2000			IL-6 higher release after OR when compared with those of EVAR group
Boyle et al. [46]	2000			
Galle et al. [47]	2000	Both	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.
			TNF-α	No statistically significant tendency toward early acute TNF-α production in EVAR and no TNF-α production in OR.
Marjanovic et al. [83]	2011	Both	IL-6	In EVAR group the "normalization" of its values came early in the 2nd postoperative day
Yates et al. [52]	2011	EVAR	IL-1α	EVAR surgical intervention significantly decreases IL-1α

which in turn may contribute to infectious complications and sepsis, the most common cause of late death after trauma. Strong stimulation of the sympathetic/adrenomedullary system and the hypothalamic-pituitary-adrenal (HPA) axis correlates with the severity of injury and poor prognosis [35, 54, 55]. The simultaneous activation of these two systems allows the organism to adapt and maintain or regain homeostasis during stress. Stress induced activation of the HPA axis is produced by activation of suprahypothalamic brain structures that release hypothalamic corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) [54].

During major abdominal procedure, plasma levels of CRH and corticotropin are remarkably higher, demonstrating a pulsatile pattern, compared with continuous one of those observed during neck surgery [53]. Schulte et al. [56] further evaluated the discrete CRH, corticotropin and cortisol pulsatility during major surgery concluding that the pathophysiology generating the pattern of CRH, corticotropin and cortisol secretion in surgical stress due

to major surgery need to be elucidated because CRH changes alone could not justify neither the circadian rhythm nor the pulsatility of corticotropin and cortisol. The stronger activation of the HPA axis during abdominal surgery should be attributed to the more extensive trauma and greater blood loss [53].

In addition, Witorsch and Brodish [57] proposed that other factors could activate the HPA axis during surgical stress, demonstrating an endogenous corticotropin-releasing activity ("tissue CRFs"), when being liberated in bloodstream by the traumatized tissue during surgery. Substances with these properties are, among others, IL-l, IL-6, interferon gamma (INF-γ), and TNF-α [58], whose involvement in surgical stress has already been described in our review. Gillies et al. [59] proposed that AVP could also partly explain the higher levels of corticotropin in the systemic circulation during surgical stress, as a result of the known synergism between this hormone and CRH on corticotropin secretion.

Epinephrine-norepinephrine

Whereas considerable work has been done comparing the immunologic response in patients undergoing EVAR and OR surgery, there has been little investigation of the release of epinephrine and norepinephrine in these two groups.

Plasma epinephrine concentrations increased during OR ($p < 0.05$) and were greater than in the EVAR group ($p < 0.05$). Plasma norepinephrine concentrations increased during surgery in both groups but the changes were not statistically significant [17, 19, 60].

Kataja et al. [61] found significantly lower plasma norepinephrine levels in the EVAR group compared to the OR group ($p = 0.048$). Plasma epinephrine decreased intraoperatively ($p = 0.001$) from the preanesthetic value in the EVAR group [61].

It is also suggested that higher epinephrine levels are correlated with complications, a finding that is indicative of the property of stress hormones to be primary, nonspecific markers of organ compromise and ability of human body to respond to infectious and inflammatory challenges [62].

Glucocorticoids

Glucocorticoids are necessary for host to tolerate surgical stress [63]. One of their actions is the prevention of overreaction to the stressful stimuli [64]. Glucocorticoids are also associated with undesired immunosuppression, electrolyte imbalance and delayed wound healing [65, 66].

It is shown that during major surgical procedure plasma corticotropins increase steadily with clear elevations seen 45 minutes after the onset of surgery ($p < 0.001$) [53] and are correlated with those of cortisol ($p < 0.001$) [53]. Plasma cortisol in turn, increased steadily, with clear elevations seen 60 minutes after the onset of surgery, reaching highest levels toward the end of the surgical procedure ($p < 0.00l$) [53]. Pearson et al. [60] compared an OR and an EVAR group undergoing AAA repair and reported a significant increase in cortisol ($p < 0.001$) [19, 60] in all patients, with the OR group demonstrating the highest levels. Salartash et al. [19] also highlighted that cortisol may be a more important factor than previously recognized in characterizing a greater early stress response associated with OR. In the same tone, Kataja et al. [61] found that postoperative levels of cortisol were higher in the OR group rather than the EVAR group.

Following major surgery in general, elevated cortisol is associated with high ACTH [67]. A dissociation between ACTH (low) and cortisol (high) is observed, which is attributed to increased adrenal responsiveness to ACTH [67]. In a recent meta-analysis it is shown that patients receiving intravenous glucocorticoids were 24% less likely to suffer postoperative morbidity compared with controls [68]. In addition, steroids significantly reduced postoperative blood levels of inflammatory markers such as IL-6. Interestingly, there was no risk difference in infectious complications and wound healing [68].

Arginine vasopressin (AVP)

Miltenberger and Moran [69] and Moran et al. [70] were pioneers in investigating the plasma AVP concentrations during surgical stress in major procedures in the abdominal cavity, reporting that upper abdominal visceral manipulation [69] and pain [70] could be potent

Table 2. The role of hormones in AAA repair-related surgical stress

Author	Year	Procedure	Cytokine	Findings
Thompson et al. [17]	1999	Both	Epinephrine and norepinephrine	Plasma epinephrine concentrations increased during (OR) and were greater than in the EVAR group. Plasma norepinephrine concentrations increased during surgery in both groups but the changes were not statistically significant. Similar results with the above as far as epinephrine and norepinephrine are concerned.
Salartash et al. [19]	2001		Epinephrine, norepinephrine and cortisol	In both groups there was a significant increase in cortisol with the OR group demonstrating the highest levels.
Pearson et al. [60]	2005			
Kataja et al. [61]	2007	Both	Epinephrine, norepinephrine and cortisol	Significantly lower plasma norepinephrine levels in the EVAR group as compared to the OR group. Plasma epinephrine decreased intraoperatively from the preanesthetic value in the EVAR. Postoperative levels of cortisol were higher in the OR group rather than the EVAR group.
Carvalho et al. [71]	2011	OR	AVP	Plasmatic AVP levels were increased at the first six postoperative hours, decreasing thereafter, but remaining above basal values.

stimuli to increase AVP release. Calogero et al. [53] demonstrated that plasma AVP levels increase after 60 minutes of the onset of a major surgical procedure. They maintain high levels during the first postoperative day and return to normal the next day ($p < 0.00l$) [53]. These higher levels of AVP during major abdominal procedure are attributed to greater fluid shifts compared to neck surgery [53].

In cases of AAA repair, plasma AVP levels increased in the first six postoperative hours, decreasing thereafter, but remaining above normal until the 2nd postoperative day and normalizing 72 h postoperatively [71]. The natural course of AVP changes presents only in uncomplicated cases [70] and although its pathophysiologic mechanisms have not yet been fully elucidated [72], it can be influenced by the type [73] and invasiveness [74] of the surgical procedure, the type of anesthesia [72] and by hemodynamic and/or serum osmolarity alterations in the peri-operative period [72]. Considering that no correlations were found between AVP levels and hemodynamic or plasmatic osmolarity variations in AAA repair, it seems that stress response is mainly secondary to hazardous stimulation mediated by the autonomic nervous system that is not completely blocked by anesthetics [71].

Table 2 summarizes the role of hormones in AAA repair-related surgical stress.

Discussion

Immunomodulatory functions are essential for homeostasis but overactivation of the neuroendocrine stress axis may render a host immunosuppressed and susceptible to infectious disease [62]. This concept may have as a result that a greater stress response to surgery may lead to less systemic inflammation of host but more susceptibility to infectious complications. On the other hand, Mulla et al. [75] oppose to this concept, because it was shown that the occurrence of SIRS or sepsis was associated with a greater stress response, that could be attributed to the activation of a branch of the neuroendocrine-immune regulatory loop in which pro-inflammatory cytokines released in response to an insult stimulate the HPA axis, thus provoking the release of glucocorticoids. Additionally, the correlation of higher epinephrine levels and the occurrence of SIRS/sepsis consort with the concept of catecholamine induced suppression of specific pro-inflammatory cytokines [60].

One parameter that seems predictive of increased activation of the stress response is the length of operation, irrespective of anesthetic method. Procedures and patients with operative times greater than 5 hours developed significantly higher CRP, IL-1beta, IL-6, and TNF-alpha levels ($p < 0.05$) at 12 and 24 hours postoperatively than those with total operative

times less than 4 hours [76], which is normally the case in AAA repair. For this reason it is not absurd to consider that approaches with less operative time or blood loss should gain ground.

Several studies have compared the inflammatory responses associated with each method of AAA repair by using a variety of markers with sometimes conflicting results. Pearson et al. [60] demonstrated a significantly higher incidence of SIRS/sepsis after OR compared with the EVAR group [60]. Inflammatory markers demonstrated to be present at greater levels after the OR compared with EVAR include the pro-inflammatory cytokines IL-6 [18] and IL-8 [18], C-reactive protein [47] indicators of T-lymphocyte activation [47] and complement activation products [47]. Conversely, Morikage et al. [77] noted that levels of IL-6, C-reactive protein and leukocytes were higher among patients undergoing EVAR compared with OR. Hence, they concluded that EVAR provoked a greater biological response. Other indicators of inflammatory processes, including levels of neutrophil and platelet degranulation products, have failed to distinguish between the two approaches to aneurysm repair [45]. Similarly, Sweeney et al. [78] found that the use of SIRS criteria failed to detect a difference between the two approaches to repair in a small patient cohort. Kruimel et al [79] evaluated the relationship between immune and neuroendocrine responses in patients undergoing OR at pre-, intra- and postoperative periods. AVP and ACTH plasma levels have significantly increased during the intra-operative period, but cortisol levels did not change. These findings suggested that glucocorticoids are not a key-factor for the depression in the production and releasing of pro-inflammatory cytokines. Barbieri et al. [80] found that after EVAR, patients who experienced less pain showed a more intense prolactin (PRL) response while cortisol response did not differ statistically significantly.

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 morbidity, mortality and length of hospital stay [81, 82].

Conclusions

Despite consistent development of clinical signs of SIRS and spontaneous release of IL-6, AAA repair produces a state of impaired pro-inflammatory cytokine response. A greater inflammatory response to OR may reflect the extent of mechanical tissue injury and the magnitude of ischemic-reperfusion injury. The greater incidence of complications after OR could be attributed to the abundant literature on this topic. Literature highlights no statistically significant tendency toward early acute TNF-α production in EVAR and no TNF-α production in OR. IL-6 and IL-8 levels are higher after OR especially when compared with those of EVAR. IL-10 peak was observed during ischemic phase in aneurysm surgical repair with peak IL-10 plasma levels in TAAA repair being significantly higher compared to those seen during AAA repair. This could be attributed to the more extensive surgical maneuvers in TAA repair (thoracotomy and retroperitoneal abdominal approach) as well as to more extensive ischemia (spinal and visceral ischemia).

As far as hormones are concerned, cortisol and epinephrine levels are higher in OR group in comparison to EVAR. AVP levels during AAA repair are related to stress response, secondary to hazardous stimulation mediated by the autonomic nervous system. Finally, the incidence of SIRS, sepsis and all complications was significantly higher in OR than EVAR patients and oxidative stress during AAA repair is thought to be higher in cases of OR beside EVAR and in cases with ruptured AAAs beside elective cases.

Disclosure of conflict of interest

No conflicts of interest declared.

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References

[1] Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109-117.
[2] Swartbol P, Truedsson L and Norgren L. The inflammatory response and its consequence for the clinical outcome following aortic aneurysm repair. Eur J Vasc Endovasc Surg 2001; 21: 393-400.
[3] Froon AH, Greve JW, Van der Linden CJ and Buurman WA. Increased concentrations of cytokines and adhesion molecules in patients after repair of abdominal aortic aneurysm. Eur J Surg 1996; 162: 287-296.

[4] Groeneveld AB, Raijmakers PG, Rauwerda JA and Hack CE. The inflammatory response to vascular surgery-associated ischaemia and reperfusion in man: effect on postoperative pulmonary function. Eur J Vasc Endovasc Surg 1997; 14: 351-359.
[5] Barry MC, Kelly C, Burke P, Sheehan S, Redmond HP and Bouchier-Hayes D. Immunological and physiological responses to aortic surgery: effect of reperfusion on neutrophil and monocyte activation and pulmonary function. Br J Surg 1997; 84: 513-519.
[6] Welbourn CR, Goldman G, Paterson IS, Valeri CR, Shepro D and Hechtman HB. Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil. Br J Surg 1991; 78: 651-655.
[7] Tang L, Ugarova TP, Plow EF and Eaton JW. Molecular determinants of acute inflammatory responses to biomaterials. J Clin Invest 1996; 97: 1329-1334.
[8] Davies MG and Hagen PO. Systemic inflammatory response syndrome. Br J Surg 1997; 84: 920-935.
[9] Holzheimer RG, Gross J and Schein M. Pro- and anti-inflammatory cytokine-response in abdominal aortic aneurysm repair: a clinical model of ischemia-reperfusion. Shock 1999; 11: 305-310.
[10] Bengtson A and Heideman M. Altered anaphylatoxin activity during induced hypoperfusion in acute and elective abdominal aortic surgery. J Trauma 1986; 26: 631-637.
[11] Gadaleta D, Fantini GA, Silane MF and Davis JM. Neutrophil leukotriene generation and pulmonary dysfunction after abdominal aortic aneurysm repair. Surgery 1994; 116: 847-852.
[12] Arndt P and Abraham E. Immunological therapy of sepsis: experimental therapies. Intensive Care Med 2001; 27 Suppl 1: S104-115.
[13] Berridge DC, Chamberlain J, Guy AJ and Lambert D. Prospective audit of abdominal aortic aneurysm surgery in the northern region from 1988 to 1992. Northern Vascular Surgeons Group. Br J Surg 1995; 82: 906-910.
[14] Parodi JC, Palmaz JC and Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991; 5: 491-499.
[15] May J, White GH, Yu W, Ly CN, Waugh R, Stephen MS, Arulchelvam M and Harris JP. Concurrent comparison of endoluminal versus open repair in the treatment of abdominal aortic aneurysms: analysis of 303 patients by life table method. J Vasc Surg 1998; 27: 213-220; discussion 220-211.
[16] Baxendale BR, Baker DM, Hutchinson A, Chuter TA, Wenham PW and Hopkinson BR. Haemodynamic and metabolic response to endovascular repair of infra-renal aortic aneurysms. Br J Anaesth 1996; 77: 581-585.
[17] Thompson JP, Boyle JR, Thompson MM, Strupish J, Bell PR and Smith G. Cardiovascular and catecholamine responses during endovascular and conventional abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 1999; 17: 326-333.
[18] Rowlands TE and Homer-Vanniasinkam S. Pro- and anti-inflammatory cytokine release in open versus endovascular repair of abdominal aortic aneurysm. Br J Surg 2001; 88: 1335-1340.
[19] Salartash K, Sternbergh WC 3rd, York JW and Money SR. Comparison of open transabdominal AAA repair with endovascular AAA repair in reduction of postoperative stress response. Ann Vasc Surg 2001; 15: 53-59.
[20] Thompson MM, Nasim A, Sayers RD, Thompson J, Smith G, Lunec J and Bell PR. Oxygen free radical and cytokine generation during en-dovascular and conventional aneurysm repair. Eur J Vasc Endovasc Surg 1996; 12: 70-75.
[21] Aivatidi C, Vourliotakis G, Georgopoulos S, Sigala F, Bastounis E and Papalambros E. Oxidative stress during abdominal aortic aneurysm repair--biomarkers and antioxidant's protective effect: a review. Eur Rev Med Pharmacol Sci 2011; 15: 245-252.
[22] Swartbol P, Norgren L, Albrechtsson U, Cwikiel W, Jahr J, Jonung T, Parsson H, Ribbe E, Thorne J, Truedsson L and Zdanowski Z. Biological responses differ considerably between endovascular and conventional aortic aneurysm surgery. Eur J Vasc Endovasc Surg 1996; 12: 18-25.
[23] Norgren L and Swartbol P. Biological responses to endovascular treatment of abdominal aortic aneurysms. J Endovasc Surg 1997; 4: 169-173.
[24] Norwood MG, Bown MJ, Sutton AJ, Nicholson ML and Sayers RD. Interleukin 6 production during abdominal aortic aneurysm repair arises from the gastrointestinal tract and not the legs. Br J Surg 2004; 91: 1153-1156.
[25] Boyle EM Jr, Pohlman TH, Cornejo CJ and Verrier ED. Endothelial cell injury in cardiovascular surgery: ischemia-reperfusion. Ann Thorac Surg 1996; 62: 1868-1875.
[26] Foulds S, Cheshire NJ, Schachter M, Wolfe JH and Mansfield AO. Endotoxin related early neutrophil activation is associated with outcome after thoracoabdominal aortic aneurysm repair. Br J Surg 1997; 84: 172-177.
[27] Fiane AE, Videm V, Lingaas PS, Heggelund L, Nielsen EW, Geiran OR, Fung M and Mollnes TE. Mechanism of complement activation and its role in the inflammatory response after thoracoabdominal aortic aneurysm repair. Circulation 2003; 108: 849-856.
[28] Welborn MB, Oldenburg HS, Hess PJ, Huber TS, Martin TD, Rauwerda JA, Wesdorp RI, Espat NJ,

Copeland EM 3rd, Moldawer LL and Seeger JM. The relationship between visceral ischemia, proinflammatory cytokines, and organ injury in patients undergoing thoracoab-dominal aortic aneurysm repair. Crit Care Med 2000; 28: 3191-3197.

[29] Hanssen SJ, Derikx JP, Vermeulen Windsant IC, Heijmans JH, Koeppel TA, Schurink GW, Buurman WA and Jacobs MJ. Visceral injury and systemic inflammation in patients undergoing extracorporeal circulation during aortic surgery. Ann Surg 2008; 248: 117-125.

[30] Peveri P, Walz A, Dewald B and Baggiolini M. A novel neutrophil-activating factor produced by human mononuclear phagocytes. J Exp Med 1988; 167: 1547-1559.

[31] Kunihara T, Kubota S, Shiiya N, Iizuka K, Sasaki S, Wakasa S, Matsuzaki K and Matsui Y. Cytokine balance in hepatosplanchnic system during thoracoabdominal aortic aneurysm repair. J Artif Organs 2011; 14: 192-200.

[32] Parodi JC, Ferreira LM, Fornari MC, Berardi VE and Diez RA. Neutrophil respiratory burst activity and pro- and anti-inflammatory cytokines in AAA surgery: conventional versus endoluminal treatment. J Endovasc Ther 2001; 8: 114-124.

[33] Shindo S, Kubota K, Kojima A and Matsumoto M. A comparison of the inflammatory response and the recovery of bowel function between trans- and extraperitoneal approaches of abdominal aortic aneurysmectomy. Int Angiol 2005; 24: 355-358.

[34] O'Sullivan ST, Lederer JA, Horgan AF, Chin DH, Mannick JA and Rodrick ML. Major injury leads to predominance of the T helper-2 lym-phocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. Ann Surg 1995; 222: 482-490; discussion 490-482.

[35] Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schoning B, Glockner F, Lanksch WR, Volk HD and Docke WD. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. Nat Med 1998; 4: 808-813.

[36] Ziegenfuss T, Wanner GA, Grass C, Bauer I, Schuder G, Kleinschmidt S, Menger MD and Bauer M. Mixed agonistic-antagonistic cytokine response in whole blood from patients undergoing abdominal aortic aneurysm repair. Intensive Care Med 1999; 25: 279-287.

[37] Oldenburg HS, Burress Welborn M, Pruitt JH, Boelens PG, Seeger JM, Martin TD, Wesdorp RI, Rauwerda JA, van Leeuwen PA and Moldawer LL. Interleukin-10 appearance following thoraco-abdominal and abdominal aortic aneurysm repair is associated with the duration of visceral ischaemia. Eur J Vasc Endovasc Surg 2000; 20: 169-172.

[38] Bown MJ, Nicholson ML, Bell PR and Sayers RD. Cytokines and inflammatory pathways in the pathogenesis of multiple organ failure following abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2001; 22: 485-495.

[39] Huber TS, Gaines GC, Welborn MB 3rd, Rosenberg JJ, Seeger JM and Moldawer LL. Anticytokine therapies for acute inflammation and the systemic inflammatory response syndrome: IL-10 and ischemia/reperfusion injury as a new paradigm. Shock 2000; 13: 425-434.

[40] Syk I, Brunkwall J, Ivancev K, Lindblad B, Montgomery A, Wellander E, Wisniewski J and Risberg B. Postoperative fever, bowel ischaemia and cytokine response to abdominal aortic aneurysm repair--a comparison between endovascular and open surgery. Eur J Vasc Endovasc Surg 1998; 15: 398-405.

[41] Komori K, Ishida M, Matsumoto T, Kume M, Ohta S, Takeuchi K, Onohara T and Sugimachi K. Cytokine patterns and the effects of a preoperative steroid treatment in the patients with abdominal aortic aneurysms. Int Angiol 1999; 18: 193-197.

[42] Febbraio MA, Ott P, Nielsen HB, Steensberg A, Keller C, Krustrup P, Secher NH and Pedersen BK. Hepatosplanchnic clearance of inter-leukin-6 in humans during exercise. Am J Physiol Endocrinol Metab 2003; 285: E397-402.

[43] Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW and Goris RJ. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993; 218: 769-776.

[44] Cabie A, Farkas JC, Fitting C, Laurian C, Cormier JM, Carlet J and Cavaillon JM. High levels of portal TNF-alpha during abdominal aortic surgery in man. Cytokine 1993; 5: 448-453.

[45] Odegard A, Lundbom J, Myhre HO, Hatlinghus S, Bergh K, Waage A, Bjerve KS, Mollnes TE, Aadahl P, Lie TA and Videm V. The inflammatory response following treatment of abdominal aortic aneurysms: a comparison between open surgery and endovascular repair. Eur J Vasc Endovasc Surg 2000; 19: 536-544.

[46] Boyle JR, Goodall S, Thompson JP, Bell PR and Thompson MM. Endovascular AAA repair attenuates the inflammatory and renal responses associated with conventional surgery. J Endovasc Ther 2000; 7: 359-371.

[47] Galle C, De Maertelaer V, Motte S, Zhou L, Stordeur P, Delville JP, Li R, Ferreira J, Goldman M, Capel P, Wautrecht JC, Pradier O and Dereume JP. Early inflammatory response after elective abdominal aortic aneurysm repair:

a comparison between endovascular procedure and conventional surgery. J Vasc Surg 2000; 32: 234-246.
[48] Seekamp A, Warren JS, Remick DG, Till GO and Ward PA. Requirements for tumor necrosis factor-alpha and interleukin-1 in limb ische-mia/reperfusion injury and associated lung injury. Am J Pathol 1993; 143: 453-463.
[49] Swartbol P, Truedsson L and Norgren L. Adverse reactions during endovascular treatment of aortic aneurysms may be triggered by in-terleukin 6 release from the thrombotic content. J Vasc Surg 1998; 28: 664-668.
[50] Bown MJ, Horsburgh T, Nicholson ML, Bell PR and Sayers RD. Cytokines, their genetic polymorphisms, and outcome after abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2004; 28: 274-280.
[51] Chen CJ, Kono H, Golenbock D, Reed G, Akira S and Rock KL. Identification of a key pathway required for the sterile inflammatory re-sponse triggered by dying cells. Nat Med 2007; 13: 851-856.
[52] Yates CM, Abdelhamid M, Adam DJ, Nash GB, Bradbury AW and Rainger GE. Endovascular aneurysm repair reverses the increased titer and the inflammatory activity of interleukin-1alpha in the serum of patients with abdominal aortic aneurysm. J Vasc Surg 2011; 54: 497-503.
[53] Calogero AE, Norton JA, Sheppard BC, Listwak SJ, Cromack DT, Wall R, Jensen RT and Chrousos GP. Pulsatile activation of the hypotha-lamic-pituitary-adrenal axis during major surgery. Metabolism 1992; 41: 839-845.
[54] Axelrod J and Reisine TD. Stress hormones: their interaction and regulation. Science 1984; 224: 452-459.
[55] Naito Y, Fukata J, Tamai S, Seo N, Nakai Y, Mori K and Imura H. Biphasic changes in hypothalamo-pituitary-adrenal function during the early recovery period after major abdominal surgery. J Clin Endocrinol Metab 1991; 73: 111-117.
[56] Schulte HM, Chrousos GP, Gold PW, Booth JD, Oldfield EH, Cutler GB Jr and Loriaux DL. Continuous administration of synthetic ovine corticotropin-releasing factor in man. Physiological and pathophysiological implications. J Clin Invest 1985; 75: 1781-1785.
[57] Witorsch RJ and Brodish A. Evidence for acute ACTH release by extrahypothalmic mechanisms. Endocrinology 1972; 90: 1160-1167.
[58] Sapolsky R, Rivier C, Yamamoto G, Plotsky P and Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 1987; 238: 522-524.
[59] Gillies GE, Linton EA and Lowry PJ. Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. Nature 1982; 299: 355-357.
[60] Pearson S, Hassen T, Spark JI, Cabot J, Cowled P and Fitridge R. Endovascular repair of abdominal aortic aneurysm reduces intraoperative cortisol and perioperative morbidity. J Vasc Surg 2005; 41: 919-925.
[61] Kataja J, Chrapek W, Kaukinen S, Pimenoff G and Salenius JP. Hormonal stress response and hemodynamic stability in patients undergoing endovascular vs. conventional abdominal aortic aneurysm repair. Scand J Surg 2007; 96: 236-242.
[62] Sternberg EM. Neuroendocrine regulation of autoimmune/inflammatory disease. J Endocrinol 2001; 169: 429-435.
[63] Udelsman R, Ramp J, Gallucci WT, Gordon A, Lipford E, Norton JA, Loriaux DL and Chrousos GP. Adaptation during surgical stress. A re-evaluation of the role of glucocorticoids. J Clin Invest 1986; 77: 1377-1381.
[64] Munck A, Guyre PM and Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984; 5: 25-44.
[65] Ehrlich HP and Hunt TK. Effects of cortisone and vitamin A on wound healing. Ann Surg 1968; 167: 324-328.
[66] Simmons PS, Miles JM, Gerich JE and Haymond MW. Increased proteolysis. An effect of increases in plasma cortisol within the physiologic range. J Clin Invest 1984; 73: 412-420.
[67] Dimopoulou I, Tzanela M, Vassiliadi D, Mavrou I, Kopterides P, Orfanos S, Kotanidou A, Kontogiannopoulou S, Vasdekis S, Tsangaris I, Armaganidis A, Macheras A, Ilias I, Kostopanagiotou G and Tsagarakis S. Pituitary-adrenal responses following major abdominal surgery. Hormones (Athens) 2008; 7: 237-242.
[68] Orci LA, Toso C, Mentha G, Morel P and Majno PE. Systematic review and meta-analysis of the effect of perioperative steroids on is-chaemia-reperfusion injury and surgical stress response in patients undergoing liver resection. Br J Surg 2013 Apr; 100: 600-9.
[69] Miltenberger FW and Moran WH Jr. Peripheral Blood Levels of Vasopressin (Adh) during Surgical Procedures. Surg Forum 1963; 14: 54-55.
[70] Moran WH Jr, Miltenberger FW, Shuayb WA and Zimmermann B. The Relationship of Antidiuretic Hormone Secretion to Surgical Stress. Surgery 1964; 56: 99-108.
[71] Carvalho AC, Guillaumon AT, Cintra Ede A, de Figueiredo LC, Moreira MM and Araujo S. Plasmatic vasopressin in patients undergoing conventional infra-renal abdominal aorta aneurysm repair. Rev Bras Cir Cardiovasc 2011; 26: 404-412.
[72] Goldmann A, Hoehne C, Fritz GA, Unger J, Ahlers O, Nachtigall I and Boemke W. Combined

vs. Isoflurane/Fentanyl anesthesia for major abdominal surgery: Effects on hormones and hemodynamics. Med Sci Monit 2008; 14: CR445-452.
[73] Melville RJ, Forsling ML, Frizis HI and LeQuesne LP. Stimulus for vasopressin release during elective intra-abdominal operations. Br J Surg 1985; 72: 979-982.
[74] Donald RA, Perry EG, Wittert GA, Chapman M, Livesey JH, Ellis MJ, Evans MJ, Yandle T and Espiner EA. The plasma ACTH, AVP, CRH and catecholamine responses to conventional and laparoscopic cholecystectomy. Clin Endocrinol (Oxf) 1993; 38: 609-615.
[75] Mulla A and Buckingham JC. Regulation of the hypothalamo-pituitary-adrenal axis by cytokines. Baillieres Best Pract Res Clin Endocrinol Metab 1999; 13: 503-521.
[76] Norman JG and Fink GW. The effects of epidural anesthesia on the neuroendocrine response to major surgical stress: a randomized prospective trial. Am Surg 1997; 63: 75-80.
[77] Morikage N, Esato K, Zenpo N, Fujioka K and Takenaka H. Is endovascular treatment of abdominal aortic aneurysms less invasive regarding the biological responses? Surg Today 2000; 30: 142-146.
[78] Sweeney KJ, Evoy D, Sultan S, Coates C, Moore DJ, Shanik DG, Kell MR and Reynolds JV. Endovascular approach to abdominal aortic aneurysms limits the postoperative systemic immune response. Eur J Vasc Endovasc Surg 2002; 23: 303-308.
[79] Kruimel JW, Pesman GJ, Sweep CG, van der Vliet JA, Liem T, Jansen JB, van der Meer JW and Naber AH. Depression of plasma levels of cytokines and ex-vivo cytokine production in relation to the activity of the pituitary-adrenal axis, in patients undergoing major vascular surgery. Cytokine 1999; 11: 382-388.
[80] Barbieri A, Giuliani E, Genazzani A, Baraldi E, Ferrari A, D'Amico R and Coppi G. Analgesia and endocrine surgical stress: effect of two analgesia protocols on cortisol and prolactin levels during abdominal aortic aneurysm endovascular repair. Neuro Endocrinol Lett 2011; 32: 526-529.
[81] Tang T, Walsh SR, Fanshawe TR, Gillard JH, Sadat U, Varty K, Gaunt ME and Boyle JR. Estimation of physiologic ability and surgical stress (E-PASS) as a predictor of immediate outcome after elective abdominal aortic aneurysm surgery. Am J Surg 2007; 194: 176-182.
[82] Tang TY, Walsh SR, Fanshawe TR, Seppi V, Sadat U, Hayes PD, Varty K, Gaunt ME and Boyle JR. Comparison of risk-scoring methods in predicting the immediate outcome after elective open abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 2007; 34: 505-513.
[83] Marjanovic I, Jevtic M, Misovic S, Vojvodic D, Zoranovic U, Rusovic S, Sarac M and Stanojevic I. [Early inflammatory response following elective abdominal aortic aneurysm repair: a comparison between endovascular procedure and conventional, open surgery]. Vojnosanit Pregl 2011; 68: 948-955.