The Inflammatory Response and its Consequence for the Clinical Outcome Following Aortic Aneurysm Repair

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Objective: to review published studies on the outcome of the inflammatory response after abdominal aortic aneurysm (AAA) repair.

Methods: a literature search on PubMed was performed. All studies that determined the inflammatory response (cytokine release) after AAA repair were included. The results of the studies and differences between open and endoluminal repair were compared and evaluated.

Results: seventeen studies were identified. In most studies the investigated cytokines were TNF-α and IL-6. Determination of IL-1β, IL-8, TNFsr1 and TNFsr2 were less often performed. TNF-α may reflect, but not strictly predict, the clinical outcome in patients with ruptured AAA. IL-6 levels correlate well with the surgical trauma per se. Variations in recorded cytokine release during endovascular AAA repair may depend on the times of blood sampling.

Conclusion: both open and endovascular AAA repair provoke a cytokine response. This response is greater during open repair than during endovascular aortic aneurysm exclusion.

Key Words: Cytokines; Abdominal aortic aneurysm; Endovascular.

Introduction

Advances in modern immunological techniques have enabled the determination of both plasma- and intercellular components of the inflammatory response caused by surgical trauma. In particular, cytokines have been studied to demonstrate the severity of surgical tissue injury.

Surgical injury leads to a multifactorial perioperative response including activation of complement, coagulation, fibrinolytic and kallikrein cascades, activation of white blood cells (WBC) with degranulation and protease enzyme release, production of free radicals and synthesis of various cytokines.1

The WBCs are the key effector cells that are rapidly mobilised to heal devitalised tissue and to prevent secondary microbial invasion. WBC recruitment involves a series of events regulated by several adhesion molecules, including the CD11b/CD18 and ICAM-1 integrins, at the surface of both WBC and endothelial cells.2 Upon activation by surgical trauma there is a release of cytokines and transepithelial migration of the WBC to the injured tissue. Cytokines facilitate communication between cells involved in immunity and inflammation and are considered to play an essential role in regulating the amplitude and duration of the inflammatory response.3

The response of cytokines to trauma might be divided in three phases.4 In the first phase there is a local production of cytokines to neutralise the trauma stimulus and initiate healing and repair. In the second phase, small amounts of the cytokines are present in the systemic circulation, which help to optimise the defence mechanism. In the third phase the circulating amount of cytokines is higher than required for the repair process, leading to an abnormal inflammatory response. This may result in an extensive endothelial injury by both the direct effect of the mediators and WBC-endothelial interaction. This is characterised by generalised endothelial cell swelling, capillary leak, oedema and organ dysfunction,5–8 and manifests clinically as a systemic inflammatory response syndrome.
(SIRS), which may be followed by multiple organ failure (MOF), whereby the function of the kidneys and lungs are compromised first. As yet, the clinical importance of a transient SIRS is unclear.

The inflammatory response is complex and not only dependent on the surgical trauma. Anaesthesia and drugs, aortic clamping, visceral ischaemia, reperfusion and large volume blood transfusion injury may affect the perioperative cytokine response pattern.

This review will primarily focus upon the cytokine response and its relevance to clinical outcome following abdominal aortic aneurysm (AAA) surgery. One of the reasons to review cytokines is the conflicting data presented in the literature. An overview of the clinical studies might give a better understanding of the surgically induced inflammatory response.

Cytokines

Cytokines are low molecular weight proteins that are potent at low concentrations. After binding to specific cell surface receptors the cytokines initiate multiple effects, some of which include synthesis of other cytokines. There is also significant overlap in bioactivity of different cytokines.9

Cytokines are broadly classified as growth factors (e.g. platelet derived growth factor (PDGF), transforming growth factor (TGF-β)), chemotactic cytokines (or chemokines) (e.g. interleukin (IL)-5, IL-8), modulators of lymphocyte function (e.g. IL-2, IL-4) and modulators of an inflammatory response (e.g. IL-1β, tumour necrosis factor-alpha (TNF-α), IL-6).

Although members of the pro-inflammatory cytokine cascade play a critical role in the pathogenesis of the host response to injury, they do not act in isolation, either from each other or from other components of the inflammatory response.

The recent discovery of naturally occurring soluble receptors for TNF-α (sTNFr1, sTNFr2), a competitive antagonist for IL-1 (IL-1ra) and true anti-inflammatory cytokines such as IL-10, IL-4, and IL-13 has led to the concept of “cytokine balance”.10

The anti-inflammatory cytokines block the process or at least suppress the intensity of the cascade. Therefore, a “balance” between the effects of pro-inflammatory and anti-inflammatory cytokines is thought to determine the outcome of disease.11

Response to Ruptured Abdominal Aortic Aneurysms (AAA)

The development of MOF following ruptured AAA repair may account for more than 90% of late deaths.12 Although the pathology is not fully understood, several factors may attribute to SIRS and MOF. The majority of patients undergoing acute surgery for a ruptured AAA often suffer significant blood loss necessitating transfusions, which cause specific harmful host responses. In addition, these acute patients will normally be deprived of nutrition. Hypotension is common before and during acute aortic surgery, whereas restoration of flow leads to ischaemia-reperfusion injury.

Ischaemic injury to the large intestine may result after aortic cross clamping and is more likely after surgery for ruptured aneurysm and ligation of a patent inferior mesenteric artery. Normal colonic mucosa provides an effective barrier to pathogenic intestinal microorganisms, but even transient ischaemia may be sufficient to allow translocation of endotoxin from the lumen.13 This tends to a SIRS and may contribute to the development of MOF. Furthermore, part of the intestinal ischaemia may be a consequence of release of vasoactive agents due to intestinal manipulation and mesenteric traction during transperitoneal dissection.14 The generation of these vasoactive agents can induce splanchic ischaemia with subsequent disruption of mucosal integrity and increased intestinal permeability.15 By using an extraperitoneal approach, traction on the mesentery is absent or minimised. Lau et al.16 demonstrated an increase in intestinal permeability and a greater degree of portal endotoxaemia during transperitoneal approach to the aorta as compared to an extraperitoneal approach. Endotoxaemia occurring in relation to low sigmoid pH during and after aortic aneurysm repair has been reported.17 Experimental endotoxaemia achieved by injection of E. coli into humans has induced fever, cytokinaemia and several haematological and endocrinological effects, which are characteristic of infection and inflammation.18,19 Elevated levels of IL-1β and TNF-α have been recorded in relationship to endotoxaemia.19,20

Besides aortic cross-clamping and mesenteric manipulation, revascularisation of ischaemic lower limbs may lead to remote organ injury including changes in intestinal mucosal morphology and increases in bowel permeability.21 After activation, WBC infiltrate and sequestre in the capillaries. The large contact area between endothelium and WBC will lead to sludging and plugging of the capillaries, thus obstructing blood flow. When the lower limbs are reperfused, activated WBC might in this way affect the intestinal vascularisation. Moreover, hypoperfusion can also result from redistribution of blood from the splanchnic circulation when the lower limbs are reperfused.
Table 1. Cytokine response in patients undergoing an abdominal aortic aneurysm repair (AAA).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>AAA-repair</th>
<th>No of patients</th>
<th>IL-1β↑</th>
<th>TNF-α↑↑↑</th>
<th>IL-6↑↑↑</th>
<th>IL-8↑↑↑</th>
<th>TNFsr1↑↑↑</th>
<th>TNFsr2↑↑↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baigrie et al.</td>
<td>1992</td>
<td>Conventional</td>
<td>20</td>
<td>↑</td>
<td>ND</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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<tr>
<td>Parry-Billing et al.</td>
<td>1992</td>
<td>Conventional</td>
<td>9</td>
<td>ND↑</td>
<td>ND</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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<tr>
<td>Roumen et al.</td>
<td>1993</td>
<td>Ruptured</td>
<td>20</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Froon et al.</td>
<td>1996</td>
<td>Shock</td>
<td>19</td>
<td>↑↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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<tr>
<td>Swartbol et al.</td>
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<td>Conventional</td>
<td>7</td>
<td>↑</td>
<td>ND</td>
<td>↑↑↑</td>
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<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>1996</td>
<td>Conventional</td>
<td>6</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Froon et al.</td>
<td>1996</td>
<td>Endovascular</td>
<td>19</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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<td>↑↑↑</td>
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</tr>
<tr>
<td>Syk et al.</td>
<td>1999</td>
<td>Conventional</td>
<td>14</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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</tr>
<tr>
<td>Holmberg et al.</td>
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<td>Endovascular</td>
<td>10</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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</tr>
<tr>
<td>Holzheimeier et al.</td>
<td>2000</td>
<td>Endovascular</td>
<td>10</td>
<td>↔</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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<tr>
<td>Galie et al.</td>
<td>2000</td>
<td>Endovascular</td>
<td>7</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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<tr>
<td>Ødegård et al.</td>
<td>2000</td>
<td>Conventional</td>
<td>10</td>
<td>↔</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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</tr>
<tr>
<td>Burger et al.</td>
<td>2000</td>
<td>Endovascular</td>
<td>15</td>
<td>↑↑</td>
<td>↑↑↑</td>
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<tr>
<td>Boyle et al.</td>
<td>2000</td>
<td>Conventional</td>
<td>20</td>
<td>↔</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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</tr>
<tr>
<td>Elmarasy et al.</td>
<td>2000</td>
<td>Endovascular</td>
<td>14</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>IL-1β↑, TNF-α↑, IL-6, IL-8 (pg/ml)</th>
<th>TNFsr1↑↑↑, TNFsr2 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not detectable</td>
<td>ND</td>
</tr>
<tr>
<td>↔ No change from baseline</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>Within normal limits</td>
<td>&lt;15</td>
</tr>
<tr>
<td>↑↑↑</td>
<td>&lt;1.5/&lt;3</td>
</tr>
</tbody>
</table>

| ↑↑     | 15–200 |
| ↑↑     | 200–400|
| ↑↑↑    | >400   |

* = significantly higher.

Several studies have tried to correlate the clinical outcome and inflammatory response. Plasma concentrations of IL-1β and TNF-α were found to be significantly higher in patients presenting with a ruptured AAA compared with those operated on electively22,23 (Table 1) and correlated well with the subsequent development of adult respiratory distress syndrome (ARDS) and MOF. The TNF-α values were increased during the first 2 weeks of ICU admission in patients with ARDS/MOF in the study by Roumen et al.22 Froon et al.23 observed TNF-α increase in 10 out of 19 patients in shock. Concentrations were highest on day 2 of the study period. In 34%, detectable levels were found during the 5-day course. On the other hand, Soong et al.24 sporadically detected TNF-α (peak levels within the normal range (<15 pg/ml)) in a series where survivors and non-survivors were compared (Table 1). There was, however, a significantly higher increase of TNFsr1 in the non-survivor group, although the survivor group had consistently higher mean values of TNFsr1. A possible explanation is that the laboratory method used for TNF-α measurement in this study may be inaccurate in the presence of soluble receptors of TNF-α. They might bind to an epitope detected by the antibodies. On the other hand, since it has been suggested that soluble receptors of TNF-α may limit and antagonise TNF-α activity, these results may yield information on the host’s ability to counter the effect of TNF-α production after surgically induced inflammatory response. Besides detectable TNF-α, Froon et al.23 also found increased TNFsr1 levels up till 5 days postoperatively. The preoperative concentrations of soluble TNF receptor were higher in those patients whose recovery was uneventful in this study. TNFsr might therefore be more accurate to follow the inflammatory response to surgical injury as...
Table 2. Normal plasma cytokine ranges.

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Plasma range (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemokines</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>0–10</td>
</tr>
<tr>
<td>Pro-inflammatory</td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>&lt;5</td>
</tr>
<tr>
<td>TNF-α</td>
<td>&lt;15</td>
</tr>
<tr>
<td>IL-6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td></td>
</tr>
<tr>
<td>IL-1ra</td>
<td>&lt;600</td>
</tr>
<tr>
<td>TNFsr1</td>
<td>&lt;1500</td>
</tr>
<tr>
<td>TNFsr2</td>
<td>&lt;3000</td>
</tr>
<tr>
<td>IL-10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Compared to TNF-α. The biological significance of high concentrations of natural TNF-α inhibitors is still unclear, as concentrations of these receptors are found to be 30- to 1000-fold higher than TNF-α itself (Table 2).

In all studies a significant rise of IL-6 was recorded which reflects the surgical trauma per se. Although IL-6 is elevated during postoperative complications, they do not predict the clinical outcome.

Conventional vs. Endovascular AAA Repair

Elective aortic surgery utilising synthetic graft-material, as well as studies of vascular graft materials in vitro, have shown systemic reactions and inflammatory responses. Recently, several studies have demonstrated an inflammatory response with endovascular aortic aneurysm repair. It has been suggested that minimally invasive surgery leads to lower cytokine production compared to conventional surgery as a result of lesser tissue injury. We found in a first series that endovascular aortic aneurysm repair induced a significant inflammatory response, mainly involving TNF-α and differing from the findings during open aneurysm repair. We also recorded a decreased blood pressure during insertion of the endovascular device in the majority of cases. There was a correlation between the increased level of TNF-α with subsequent significant alteration of cell surface receptors (CD11a, CD11b, CD11c, CD18 and L-selectin) at 60 min post balloon inflation. One study which addressed upregulation of adhesion molecules and release of cytokines found an increase in ICAM-1, E-selectin and P-selectin within 12–24 h after implantation of the endovascular device, while there was just a short period of moderate increase of IL-6 and IL-8.

Galle et al. failed to demonstrate upregulation of surface molecules (CD69, CD25, CD40 and CD54) in both open and endovascular AAA repair. Nor did they find any significant differences in levels of soluble VCAM-1, E-selectin and P-selectin in any group.

Conventional surgery induced responses which were more related to the extensive surgical trauma and a reperfusion injury. Endovascular treatment involves catheter manipulations inside lesser or greater parts of the vascular system with a possible subsequent endothelial injury. When excluding an aortic aneurysm it is still left in place together with its mural thrombus, and manipulations with introducers and catheters are performed inside the aneurysm in the vicinity of, or even in, the mural thrombus. The biological responses to these manoeuvres might be different from those achieved during clamping, mesenteric traction and reperfusion, routine parts of open revascularisation and could probably explain our findings. Although harmful levels of cytokines were reached during the endovascular procedures, and correlation to complications seems reasonable, this kind of transient reaction occurred also in non-complicated cases. These results suggest that cytokine levels can rise without any association with clinical parameters. Although anti-inflammatory cytokines were not measured, a rise of these anti-inflammatory cytokines might explain a transient reaction without clinical consequences. On the other hand, anti-inflammatory cytokines may serve to attenuate some of the exaggerated responses; excessive production may induce a prolonged immunosuppressed state that can also be deleterious to the host.

The mural thrombus inside the aneurysm is usually seen as “inert”, which is not correct as it is demonstrated that the thrombus contains IL-6. The hypothesis that the adverse reactions during endovascular repair of AAA in the first series were triggered by IL-6 release from the thrombotic content due to manipulations with introducers and catheters in the vicinity or in the mural thrombus could be explained by micro- or macroembolisation, but also release of toxic products and of cytokines. It is well known that bacteria, mainly Staphylococcus epidermidis, contaminate a proportion of aortic aneurysm thrombi, reported to be from 5 to 24%. Taking this low incidence into account it seems, however, less reasonable to assume that a bacteraemia explains our findings. Apparently the thrombus also may appear differently, being more or less organised. One may speculate whether fresh thrombi are more prone to cause reactions and release of cytokines. Aneurysms without or with only small thrombi and increased experience with more of a non-touch technique might
explain the limited or absent systemic inflammatory response found in a second series, since all other conditions were equal to the first series. Juvonen et al.\(^{48}\) contribute to the understanding that the aneurysm thrombus can release cytokines. They found that, in contrast to patients with coronary heart disease, those with AAA had circulating IL-1\(\beta\) and IL-6 in peripheral blood. Very low levels of TNF-\(\alpha\) were found in both groups of patients.

Syk et al.\(^{49}\) did not detect abnormal TNF-\(\alpha\) levels in the endovascular group in line with our second series. The absence of increased TNF-\(\alpha\) level was checked in this study by using ELISA from different manufacturers and by another laboratory verifying the same negative results, which most certainly excludes the explanation being variations due to the methodology used for analysis. Failure to measure a cytokine response might, however, be explained by an inappropriate measurement time point. Despite the systemic effects, plasma levels of TNF-\(\alpha\) peak and decline rapidly following the provoking stimulus, making detection difficult in the clinical setting. Only intensive blood sampling during surgery and up to the first 24 h might reveal a transient TNF-\(\alpha\) peak (Table 3). Moreover, cytokine measurements are performed in peripheral blood, but the absence of detectable cytokines in peripheral blood does not exclude a local production of cytokines in the injured or inflamed organ. Evidence for local production was demonstrated by Cabie et al.\(^{50}\) After reperfusion in abdominal aortic surgery, low systemic levels of TNF-\(\alpha\) were detected, whereas significantly higher TNF-\(\alpha\) levels were found in the portal vein system. Holmberg et al., however, did not demonstrate differences between cubital and femoral blood.\(^{50}\)

Partly contradicting this are the results from Thompson et al.\(^{32}\) In this study TNF-\(\alpha\) was detected during conventional repair but was lower in the endovascular group (Table 1). In this study no absolute values were presented, which makes any comparison difficult. Differences might be attributed to variations in blood sampling times and methodology used for the analysis.

Galle et al.\(^{35}\) found a tendency toward early acute TNF-\(\alpha\) production in patients undergoing an endovascular AAA repair, whereas no TNF-\(\alpha\) production was noted in the open repair. Two suggestions for this mechanism were described. First, they considered that inflammation during endovascular AAA repair may partly be triggered by the biomaterial itself. Polycarbonate-urethane covered their endografts, which are different from Dacron vascular grafts and the endografts used by the authors.\(^{31}\) A pilot study was performed by our group to exclude a device-related explanation for the inflammatory response, in which all components of the endovascular device were incubated with granulocytes and monocytes, respectively, and the upregulation of adhesion molecule CD11b on the cell surface was investigated. The results were also compared to the findings after standard graft materials had been incubated with WBC. All components of the endovascular device were found inert, and the limited upregulation was of the same magnitude as when using ePTFE grafts.\(^{31}\)

Secondly, Galle et al.\(^{35}\) supported the concept that restricted manipulations within the aneurysm and its intramural thrombus during insertion of the device may have the ability to minimise biological response induced by endovascular repair.

Another explanation is assumed by Ødegaard et al.\(^{36}\) Although they found no significant changes in TNF-\(\alpha\) in both open and endovascular AAA repair, they demonstrated a significant leukocyte and platelet activation. They suggested, based on the timing of activation, that this could be caused by radiographic contrast media.

Like TNF-\(\alpha\), IL-1\(\beta\) is also a pyrogen, induces hypotension, activates and promotes adherence of WBC and causes acute phase protein synthesis. Although increased levels have been demonstrated in septic patients, no correlation between concentrations and clinical outcome has been observed.\(^{20,32}\) IL-1\(\beta\) response is known to follow after the TNF-\(\alpha\) response. By sampling both early and intensely, IL-1\(\beta\) has been detected during acute, elective and endovascular aortic aneurysm repair.\(^{25,31,32,53}\) The elevation in concentration of this interleukin was noted to peak at around 2 h after initiation of the surgical insult. The early and short lasting IL-1\(\beta\) response to major surgical injury always preceded the IL-6 response. Baigrie et al.\(^{34}\) found, however, no correlation between the IL-1\(\beta\) and IL-6 responses. They suggested that the action of IL-1\(\beta\) was more local, with a less consistent overflow into the peripheral circulation than seen with IL-6.
The pattern of IL-6 production in septic patients differs considerably from that of TNF-α or IL-1β. The appearance of IL-6 in plasma is temporarily delayed compared to TNF-α and IL-1β, but is detectable for considerably longer periods of time and is more consistently seen after surgery. In all presented studies in conventional treated patients for AAA compared to endovascular treated patients, suggesting a greater degree of bowel ischaemia. This was associated with significantly greater postoperative concentrations of endotoxin. Since aortic clamping, mesenteric traction and retroperitoneal dissection are avoided during endovascular AAA repair, these results were suspected.

**Conclusion**

Aortic aneurysm repair influences the cytokine response. This response is more regularly seen during open repair as compared to endovascular aortic aneurysm exclusion.

TNF-α may reflect, but not strictly predict, the clinical outcome in patients with a ruptured aneurysm. The measurements of IL-6 correlate well with the surgical trauma per se.

Variations in recorded cytokine release during endovascular aortic aneurysm surgery may depend on the times of blood sampling. Major changes were seen 1 h after stent-graft implantation, and few studies have used sampling at this timepoint. Endovascular procedures may furthermore cause rather extensive endothelial injury due to large introducers, and as the aneurysm is left intact with its mural thrombus there is at least a theoretical risk for microembolisation due to catheter manipulations inside the aneurysm.

The release of IL-6, possibly together with other pro-inflammatory factors, enables WBC to release TNF-α. Under certain circumstances this mechanism is able to cause clinical reactions closely related to a SIRS. In patients whose aneurysm contains small or no thrombi at all, these reactions have been totally absent. Therefore, it is advisable that all efforts should be made to avoid manipulations, especially inside the aneurysm, as much as possible, both to reduce endothelial damage and to avoid fragmentation of the thrombus.

The cytokine cascade activated in response to aortic aneurysm repair consists of a complex biochemical network with diverse effects on the patient. Especially with ruptured aneurysms, IL-1β and TNF-α are pro-inflammatory cytokines which produce fever, inflammation, tissue destruction, and in some cases shock and death. It is possible to reduce the biological activities of IL-1β and TNF-α by neutralising antibodies, soluble receptors and receptor antagonists. Blocking IL-1β and TNF-α has been successful in patients with rheumatoid arthritis or inflammatory bowel disease but has not been successful in humans with sepsis.
In some studies harmful levels of cytokines were reached after the endovascular procedures. The question is whether a transient reaction without any association with clinical parameters besides long-lasting temperature increase needs any treatment? So far, long-term results after endovascular AAA repair are not available and leave this question open.

Further studies of the role played by the anti-inflammatory cytokines may provide important information and have to be performed. Furthermore, research of anticytokine therapy is essential.

References


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