Inflammatory responses after surgery

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The inflammatory response after major surgery is of great importance for patients, physicians and perioperative medicine in general. This article, although not intended to be comprehensive, provides an overview of present knowledge about inflammatory mechanisms, predictive parameters and therapeutic approaches.

Surgery leads to a wide range of changes in haemodynamic, endocrine-metabolic and immune responses. Over the past decade, a great amount of research has been performed aiming to understand in more detail the non-specific inflammatory response related to surgery.

The inflammatory response is essential for the structural and functional repair of injured tissue, as complement, granulocytes, macrophages and many other different mediators are required for appropriate wound healing. It is, however, a double-edged sword. Excessive stimulation of the inflammatory cascade may aggravate tissue damage, as seen in reperfusion injury after myocardial infarction or hepatectomy, and may lead, at least in certain groups of patients, to systemic inflammatory response syndrome, sepsis, multi-system organ failure and finally death.

To prevent this hyperinflammation and improve patients' outcome after surgical procedures, it is essential to gain more knowledge about mediators being released perioperatively and their role in the inflammatory network at cellular and even molecular levels. This may allow the modulation of certain responses through pharmacological intervention.

In general terms, inflammation can be described as a reaction of the host against injurious events, such as microorganisms, chemical or physical substances or other pathogens, aiming to quarantine and destroy the harmful invaded agents. Locally damaged endothelial cells, tissue mast cells as well as platelets induce vasodilatation and increase vascular permeability by releasing vasoactive substances, such as histamine or leukotrienes. Vasoactive components of the activated complement cascade and kinin system increase the already existing circulatory disorders and induce the release of cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL)-1 and IL-8, which direct the inflammatory response. Following plasma exudation, certain cytokines induce chemotaxis, whereupon white blood cells, especially polymorphonuclear neutrophils (PMNs) and monocytes, migrate from the vessels into the inflamed area, where they exert their microbicidal actions by releasing toxic oxygen metabolites and inducing phagocytosis.

Thus, a significant local inflammation causes a systemic response, termed the acute phase response, amplifying its signals by recruiting several different mediators and systems ranging from lipid and polypeptide mediators to inflammatory cell activation.

CYTOKINES

Recent research focuses on the role of cytokines within the inflammatory cascade, as these seem to be most prominent in conducting the response.

Cytokines, including interleukins, TNF and growth factors, are a heterogeneous group of low molecular weight proteins acting on cell surface receptors to regulate and modify cell growth, maturation and especially inflammation by stimulating gene transcription. Cytokines are released on external stimuli by various activated cells (leucocytes, in particular monocytes, fibroblasts or endothelial cells). Cytokines function in either a paracrine or autocrine manner, acting at picomolar concentrations.

As reviewed by Lin et al (2000), surgery stimulates generation of a great amount of different cytokines. Since TNF-α, IL-1, IL-6 and IL-8 are considered to be the main proinflammatory cytokines, this article will focus on them.

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TNF-α

TNF-α, widely known as cachectin, shares a central role with IL-1 in activating inflammatory mediators and cells, such as priming of PMNs or inducing production of IL-6, platelet-activating factor (PAF) and leukotrienes. Plasma levels of TNF-α increased under cardiopulmonary bypass (CPB), peaking in a bimodal fashion 2 hours and again 18–24 hours after the onset of CPB (Miller and Levy, 1997). However, other studies found only a negligible rise in plasma levels after CPB. Nevertheless, TNF-α has been shown to be among the earliest cytokines to increase after surgery, suggesting an initiating role in the inflammatory response.

IL-1

IL-1 potently induces prostaglandin E_2 production in the hypothalamus and the release of proinflammatory interleukins from activated inflammatory cells. Similar to TNF-α, plasma levels of IL-1 have been reported at times to increase after CPB, peaking 24 hours postoperatively (Miller and Levy, 1997), but again this is disputed by other studies (Royston, 1997).

IL-6

Released by a variety of stimulated cells, such as macrophages, fibroblasts and lymphocytes, IL-6 elicits a multitude of biological effects, such as antiviral activity, influencing haematopoesis and B lymphocyte activation and, most significantly, coordinating the acute phase response. As shown by Buttenschoen et al (2001), IL-6 concentrations in patients with major abdominal surgery increased significantly 2 hours postoperatively and remained elevated for another 24 hours before returning to preoperative values after 3 days postoperatively. Similar patterns for IL-6 have been described in cardiac surgery (Miller and Levy, 1997). Plasma levels increased 2 hours postoperatively, reached a peak after 4 hours and stayed significantly elevated for up to 24 hours. The magnitude of the increase in IL-6 plasma levels seems to be directly related to the degree of tissue injury.

IL-8

Acting as a potent chemoattractant and priming agent for PMNs, IL-8 is secreted by a variety of TNF-α and IL-1 stimulated cells. Cardiac surgery has been reported to increase plasma levels of IL-8 significantly, following a similar time course as IL-6, with elevation during the initiation of rewarming from hypothermia, peaking 1–3 hours postoperatively and still being detectable 24 hours later (Miller and Levy, 1997).

COMPLEMENT AND COAGULATION

As suggested by several authors over the past years, and investigated primarily in cardiac surgery patients, complement activation may act as a trigger for initiation of the inflammatory response. Indeed, Miller and Levy (1997) reported that activated complement proteins C3a and C5a are released into the circulation within the first 10 minutes after CPB, resulting in an increased production of inflammatory cytokines, e.g. IL-6, IL-1, and the release of histamine, which in turn alters vascular permeability, induces chemotaxis and activates PMNs and monocytes.

The major mechanism of complement activation was shown to be the alternative pathway, stimulated mainly by either endotoxins or contact activation induced by blood being exposed to non-physiological material surfaces of the extracorporeal circuit.

Gu et al (1999) investigated whether complement activation also occurs without the use of CPB in patients undergoing coronary artery bypass grafting (CABG). The authors reported an increase of C3a levels, suggesting that the surgical procedure itself activates the complement cascade. In agreement with previous observations, concentrations of C4a, as a marker of the classical pathway, did not increase, indicating that pure tissue injury activates complement mainly through the alternative pathway. Interestingly, the authors could further show a higher systemic inflammatory response at least in the early postoperative period, determined by the enhanced release of IL-6, C3a and the terminal complement complex C5b-9, in response to greater surgical trauma (median sternotomy *vs* lateral thoracotomy).

Activation of factor XII (Hagemann factor), and subsequently of factor XI, of the coagulation cascade by CPB implements the intrinsic coagulation cascade, resulting in thrombin generation and stimulation of the kinin system. As prekallikrein is converted into kallikrein, the classical complement pathway also becomes involved and contributes, albeit to a small extent, to the stimulation of the inflammatory response.

In conclusion, strategies for the inhibition of complement activation during cardiac surgery should address both blood–material interactions and the contribution of tissue injury.

ENDOTHELIAL CELLS AND TISSUE INJURY

As described by Boyle et al (1997), CPB and the induced activation of coagulation, complement, and the kinin system, as well as the

release of proinflammatory cytokines, have widespread stimulating effects on endothelial cells, resulting in an increased expression of adhesion molecules on the surfaces of endothelial cells, e.g. intercellular adhesion molecule (ICAM). The enhanced expression of adhesion molecules leads to the recruitment of large amounts of PMNs to the site of injury. PMNs transmigrate into affected tissue, and on stimulation, they release proteolytic enzymes and toxic oxygen metabolites, which in turn contribute to further endothelial damage. In support of these findings, Pinsky et al (1996) showed that exocytosis of P-selectin (an adhesion molecule expressed on activated endothelial cells and fibroblasts) and Weibel–Palade bodies (which store van Willebrand factor) in endothelial cells are enhanced in response to hypoxia and in human hearts during hypothermic preservation.

In addition, Valen et al (2001) reported an upregulation of gene expression of adhesion molecules (as markers for endothelial cell activation), such as CD62E and ICAM-1, after myocardial reperfusion following cardiac surgery under CPB. Activated endothelium furthermore releases proinflammatory cytokines (IL-1, IL-8) and promotes coagulation in terms of limiting the spread of the inflammatory event. This reaction of endothelial cells is instrumental in a locally limited inflammation, whereas it is ineffective or even counterproductive in a generalized inflammatory response, since it results in increased leucocyte activation and consumption of coagulation factors, thereby increasing the risk of further organ injury.

INFLAMMATORY CELLS AND SURGERY

PMNs constitute a fundamental component of the non-specific immune response, as they are rapidly recruited to the site of inflammation and respond to harmful agents by releasing proteolytic enzymes and toxic oxygen metabolites and by inducing phagocytosis. Inappropriate 'overstimulation' of PMNs as a result of increased amounts of cytokines, such as TNF-α, or other activating compounds seems to contribute to enhanced generalized inflammatory responses after surgery.

PMNs of patients undergoing CPB for CABG were directly primed for respiratory burst (increased release of superoxide anions) and showed an even enhanced primability for additional stimulation with PAF (Schwartz et al, 1998). This increase in PMN primability is most likely the result of increased plasma levels of IL-8 and IL-6, which are known priming agents for PMNs (Condliffe et al, 1998). Priming hereby refers to a process whereby the response of PMNs to a subsequent activating stimulus is potentiated. Release of oxygen metabolites is markedly enhanced when PMNs have previously been primed (Condliffe et al, 1998). The priming process has been shown to be a critical component of PMN-mediated tissue injury both in vitro and in vivo (Condliffe et al, 1998).

Shimizu et al (1999) furthermore showed that PMN-mediated endothelial cell injury, measured by increased levels of thrombomodulin and elastase activity in PMN suspension cultures, was significantly enhanced in cirrhotic patients suffering from postoperative complications after partial hepatic resection.

Another mechanism of increased PMN-related tissue injury is reported by Matsuda et al (2001), who investigated exudative PMN apoptosis in response to major abdominal surgery. Increased levels of IL-6, granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) in the drainage fluid of patients undergoing major abdominal surgery, showed a significant inverse correlation with the percentage apoptosis in exudative PMN, suggesting that apoptosis of PMNs may be delayed compared with circulating PMNs at the local site of inflammation. By increasing PMN lifespan, inhibition of PMN apoptosis may upregulate a number of PMN functions, such as production of reactive oxygen intermediates or expression of adhesion molecules (CD11b, CD18), amplifying the inflammatory response.

Besides PMNs, monocytes and macrophages also undergo functional alterations related to surgery. Redmond et al (1992) demonstrated an initial significant impairment of microbicidal killing and antigen presentation of peritoneal macrophages in mice after laparotomy. Surprisingly, both functions increased significantly on the third postoperative day, compared with control values, indicating a rebound phenomenon. However, systemic macrophage functions were not influenced by surgery at all, as shown by unaltered Kupffer cell functions throughout the whole experiment.

In contrast, monocytes and macrophages have also been shown to contribute to the inflammatory process in response to surgery. Following partial hepatectomy in rats, inhibition of Kupffer cell and spleen function, such as the release of TNF-α, modulated endotoxin-induced liver injury by decreasing PMN infiltration into the liver and indirect priming of circulating PMNs (Suzuki et al, 1996).

SURGICAL TRAUMA

In general, the greater the surgical trauma, the greater the subsequent inflammatory response. To prevent hyperinflammatory responses in patients undergoing major surgery, minimization of surgical trauma is required. As reported by Jess et al (2000), surgical trauma, evaluated by measurements of serum IL-6, was significantly lower in patients undergoing laparoscopic inguinal hernia repair compared with open inguinal hernial repair. Comparing the inflammatory response induced by oesophagectomy with that by distal gastrectomy, an operation considered less harmful, expression of CD11b (adhesion molecule) on monocytes and their release of TNF-α in response to surgery reflects the degree of surgical trauma (Aosasa et al, 2000).

However, Hamano et al (2001) reported that minimal invasive cardiac surgery, despite the small skin incision required, might cause the same stress response as conventional cardiac surgery. To really evaluate advantages of surgical techniques, large randomized clinical studies will be necessary in the future.

PREDICTIVE VALUES

Preoperatively, C-reactive protein (CRP) was shown to be the most significant predictor of postoperative infection and patients' outcome in cardiac surgery. The incidence of postoperative infection and length of hospital stay were significantly higher in patients with elevated preoperative CRP values (Fransen et al, 1999).

The role of procalcitonin as a predictive marker for postoperative infections is still under discussion. Baykut et al (2000) reported that cardiac surgery patients developing postoperative infections showed increased procalcitonin levels for up to 6 days and even an additional rise at day 4–6 postoperatively, whereas commonly used inflammatory markers like CRP decreased again after the fourth postoperative day. In contrast, Bitkover et al (2000) demonstrated procalcitonin to be unreliable in predicting postoperative infections, since its levels decreased in patients with and increased in patients without infection.

In addition, leukocyte count was suggested to be valuable as a predictive marker for major infections after surgery (Bitkover et al, 2000).

THERAPEUTIC APPROACHES

To prevent hyperinflammatory responses after major surgical procedures, multiple pharmacological approaches and modifications of, for example, extracorporeal circulation in case of cardiac surgery were undertaken. These strategies focus on the attenuation of the production and release of humoral mediators, the activation of cellular components and the decrease of blood–material interactions.

Circuit modifications include the placement of leukocyte filters, heparin-coated interiors and the use of membrane oxygenators rather than bubble oxygenators. For the latter, no difference, at least in the degree of complement activation, was reported (Miller and Levy, 1997).

Glucocorticoids, administered before the onset of CPB, were shown to reduce the release of proinflammatory cytokines (IL-6), decrease neutrophil activation and stimulate release of anti-inflammatory cytokines, such as IL-10, whereas PMN apoptosis, TNF receptor expression and complement activation were not influenced at all (Miller and Levy, 1997; Rumalla et al, 2001).

Monoclonal antibodies directed against certain cytokines, their receptors, adhesion molecules and complement proteins were considered as promising approaches to prevent overstimulation of the inflammatory cascade. As reported by Fitch et al (1999), a single chain antibody for human C5 reduced C5b-9 formation, leucocyte CD11b expression, postoperative myocardial injury and blood loss in patients undergoing CABG surgery with CPB. However, immunoglobulins solely are unlikely to reduce mortality in patients and should rather be seen as part of a multifactorial approach in the immunomodulatory therapy (Sablotzki et al, 2001).

As shown by the authors' group (Fischer et al, 2001; Hollmann et al, 2001), local anaesthetics might play an important role in attenuating hyperinflammatory responses after surgery in the future, as they affect chemotaxis and neutrophil priming.

Overall, new promising pharmacological approaches to prevent hyperinflammation in patients after surgery are on their way, but as inflammation consists of a complex network of mediators, cells and cascades, much work remains to be done.

Finally, the interested reader is referred to two excellent detailed review articles on this topic (Hall et al, 1997; Miller and Levy, 1997).

CONCLUSION

Inflammation represents a complex process, which is not elucidated in detail at present. Humoral mediators, inflammatory cells and several cascades are closely intertwined for the purpose of protecting the host from deleterious pathogens. Overstimulation in response to major surgery might have crucial effects on patients' outcome. Research therefore focuses on providing

more information about the inflammatory cascade to improve pharmacological interventions. To date, no attempt was shown to be as beneficial as desired, but various approaches are being investigated and look promising for the future. HM

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KEY POINTS

- Surgery might induce an overstimulation of the inflammatory response in some patients, resulting in systemic inflammatory response syndrome, sepsis and multi-system organ failure.
- Cytokines, especially tumour necrosis factor-α, interleukin (IL)-1, IL-6 and IL-8, are considered to regulate the inflammatory response. Plasma levels of IL-6 might reflect the degree of tissue damage.
- Polymorphonuclear neutrophil activation enhances tissue and endothelial damage by releasing toxic oxygen metabolites.
- Interactions of blood with non-physiological surfaces of cardiopulmonary bypass trigger the inflammatory response by stimulating complement.
- The extent of surgical trauma might correlate with the extent of inflammation.
- Glucocorticoids, circuit modifications, immunoglobulins and local anaesthetics are promising therapeutic interventions.
- Predictive markers for postoperative infection are C-reactive protein preoperatively and procalcitonin and leucocyte count postoperatively.

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