The impact of anesthetic management on inflammation: new insights?

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The most important development in recent years is, understanding the series of physiological changes, i.e. the neurohumoral and inflammatory stress response due to surgery (1, 2). Efforts have been made taking advantage of the precipitating factors of these physiological changes, which allows even major procedures in patients with severe complicating diseases and reduces perioperative morbidity (2). However, postoperative infection is still one of the most frequent complications in spite of advances in perioperative management (1, 2, 3).

In general, the mammalian immune system responds to any injury, i.e. surgical trauma by rapidly producing pro-inflammatory cytokines and other mediators of acute inflammation (4). After this initial inflammatory response, a compensatory anti-inflammatory response ensues. Although this response scenario may have evolved as a means to protect the injured host from the harmful effects of injury-induced inflammation, many of these antiinflammatory mediators also have strong immunosuppressive activity (5). Consecutively, the host immune response following a major surgical trauma involve various degrees of downregulation of cellular immunity, i.e. Th1/Th2 imbalance, HLA-DR expression of monocytes in the early postoperative period (3, 6) which may contribute to infectious complications after surgery.

Especially cardiac surgery with the use of cardiopulmonary bypass (CPB) induces a systemic inflammatory response syndrome (SIRS) which is associated with an unbalanced release of pro- and antiinflammatory cytokines (7,8). Cytokines are one of the dominant factors guiding the development of T-helper type 1 and 2 (Th1 and Th2) cells (9, 10), which play a major role in inflammatory responses. On one hand, an early Th1 response after cardiac surgery has been hypothesized to support the inflammatory reaction by increasing the cytokines interleukin (IL)-2, IL-12 and interferon-γ (IFN-γ) (10) reflecting the magnitude of inflammation, yet patients at the same time seem to have clinical and laboratory evidence of
immunosuppression with predisposition to infection. Increased plasma levels of IL-6 in the postoperative period were associated with an increased postoperative infection rate (11). This exaggerated and prolonged activation of the immune system after cardiac surgery can lead to an increased risk of postoperative complications and a prolonged intensive care unit (ICU) stay (7, 11) and remains a significant clinical problem. Up to 36% of cardiac surgery patients require prolonged ICU care, which is associated with multi-organ failure and a higher mortality (12). Hein et al. (13) demonstrated a significantly increased ICU and in-hospital mortality rate in patients with ICU stays > 3 days.

Anesthetics may influence the immune response indirectly through modulation of the neurohumoral response or directly by acting on immune competent cells. However, in order to fully understand the immunomodulating properties and ensuing clinical relevance of anesthetics it is necessary to investigate each agent individually and in a variety of clinical settings. Experimental and clinical studies revealed that anesthetics modify the perioperative neurohumoral and immune stress response either indirectly (via the hypothalamic-pituitary-axis (HPA) and the sympathetic nervous system) or directly (via immune cells), this means influence of the cell-and cytokine-mediated immune reactivity (14, 15).

**Intravenous and inhalational anesthetics: Propofol and Isoflurane**

Inhalational and intravenous anesthetic agents can modulate host defense indirectly by interfering with the neuronal input to the neurohumoral response or they can act directly on immune-competent cells.

**Neurohumoral response**

The neurohumoral response involves activation mainly of two core systems: the HPA axis and the sympathetic nervous system. Activation of the HPA axis by corticotrophin releasing factor results in posttranslational cleavage of proopiomelanocortin to adenocorticotrophin (ACTH) and ß-endorphin and their subsequent release into the systemic circulation (15). ACTH stimulates the adrenal cortical secretion of glucocorticoids so that circulating concentrations of cortisol are increased. Major surgery is one of the most potent activators of ACTH and cortisol secretion and increased plasma levels can be measured within a few
minutes of the start of surgery (15). Usually a feedback mechanism operates so that increased concentrations of cortisol inhibit further secretion of ACTH. This control mechanism seems to be ineffective after surgery so that concentrations of both hormones remain high. Cortisol has anti-inflammatory effects. It inhibits the accumulation of macrophages and neutrophiles into areas of inflammation and can interfere with the synthesis of inflammatory mediators indicating an interaction between the immune system and neuroendocrine system. Isoflurane anesthesia has been associated with higher serum concentrations of catecholamine and cortisol when compared with propofol anesthesia (15, 16, 17) in a variety of circumstances: in patients undergoing orthopedic surgery, plasma levels of epinephrine, norepinephrine and cortisol increased to a greater extent under isoflurane than propofol anesthesia (16); in patients undergoing cardiac surgery epinephrine, norepinephrine and cortisol plasma levels increased before the start of extracorporal circulation and the increase was greater under isoflurane than propofol anesthesia (17). Cortisol has strong immunosuppressive properties. This indicates that the stress response, as measured by activation of the systemic nervous system and the HPA-axis, is lower with intravenous anesthesia than with isoflurane anesthesia.

**In case of cardiac surgery and hyperinflammation, inhalational anesthesia might be the preferred regimen due to its immunosuppressive effects via HPA axis.**

**Cell-mediated and cytokine-mediated immune reactivity**

Experimental and clinical data support the hypothesis that propofol has only minor effects on cell- and cytokine–mediated immune reactivity in comparison to inhalational anesthesia. Inada et al. (18) compared propofol versus isoflurane anesthesia with respect to their influence on T cell-mediated immune response in patients undergoing craniotomy for unruptured aneurysm. The Th1/Th2 ratio decreased after isoflurane anesthesia until day seven after surgery while it did not change in the propofol group during the entire study period. The authors suggested that surgical induced immune perturbation is relatively obtunded following propofol anesthesia compared to isoflurane anesthesia. Experimental
data (19) supported the findings of the authors Inada et al. (18): Propofol significantly increased IFN-γ/IL-4 ratio reflecting changes in the Th1/Th2 balance (p < 0.01). It is well known that a decreased IL-6/IL-10 plasma cytokine ratio is associated with an increased risk for postoperative complication in patients undergoing major surgery (20, 21). In a previous study IL-6/IL-10 ratio was significantly decreased with isoflurane compared to propofol indicating that cytokine-mediated immune response is suppressed by isoflurane (22).

In case of cardiac surgery inhalational anesthesia might be favorable due to its attenuation of the initial proinflammatory response reflecting the magnitude of inflammation.

Mu-Opioids: Fentanyl, Sufentanil, Remifentanil

Neurohumoral response

It is long established that opioids suppress hypothalamic and pituitary hormone secretion (23). Morphine suppresses the release of corticotrophin and consequently cortisol under both normal and stress conditions resulting in hypothalamic inhibition (24). The effects of morphine and other opioids have been especially well documented in cardiac surgery (24). Large doses of morphine (4 mg kg⁻¹) inhibited cortisol release until cardiopulmonary bypass (CPB) was established. Fentanyl (100 µg kg⁻¹), sufentanil (20 µg kg⁻¹) and alfentanil (1.4 mg kg⁻¹) have also been shown to suppress pituitary hormone secretion until beginning of CPB. After the onset of CPB the physiological changes are profound and hypothalamic and pituitary responses are not completely blocked by opioids (24). High-dose opioids are capable of completely abolishing the hormonal stress response, but they carry the risk of respiratory depression and consequent prolonged ventilatory support after surgery.

Cell-mediated and cytokine-mediated immune reactivity

Apart from their neurohumoral effects, opioids are known to stimulate cell-mediated immune responses via opioid receptors on different immune cells (25). Modulation by µ-receptor agonists has been demonstrated in a range of immune cells, including macrophages, monocytes, natural killer cells and T-cells (26, 27). Morphine inhibits both in vivo and in vitro
T-cell proliferation and reduces IL-2 cytokine synthesis significantly. Exposure to morphine can result in modulation of expression of a wide range of specific genes, in particular down-regulation of pro-inflammatory gene expression (27). These effects are associated with a significant reduction in the expression of IL-2 mRNA, but the exact mechanism is unknown (27). Furthermore, Murphy et al. (28) demonstrated that morphine suppressed several components (IL-6, CD11b, CD18 and post-operative hyperthermia) of the inflammatory response to cardiac surgery with the use of CPB compared with fentanyl. For anesthesia during cardiac surgery the μ-agonists, fentanyl, sufentanil and remifentanil, are commonly used; remifentanil is widely used for fast-track cardiac surgery due to its short context-sensitive half-life, permitting more rapid emergence than fentanyl (29). In a previous study of von Dossow et al. (30), remifentanil-based analgesia changed Th1/Th2 balance to a greater extent in favour of a proinflammatory response on the first postoperative day in cardiac surgery with the use of CBP which was associated with a significantly reduced intensive care unit stay compared to the fentanyl group.

Although controversially discussed earlier, it is now clearly established that mu-opioid receptors are expressed in immune effector cells (31). This means, that their expression on immune effector cells allows immunomodulatory effects of opioids. Since several effects of these are antiinflammatory (32, 33), the use of mu-opioids may be beneficial not only to treat painful symptoms of an inflammation, but also ist cause. However, their expression is inducible, i.e. in response to cytokines. Since cytokines are expressed in immune cells in response to many stimuli, there is reason to believe that a certain number of mu-opioid receptors is normally present in immune effector cells. In addition, mu-opioid receptors are induced in response to activation of the T-cell receptor complex (34).

**In conclusion, the immunosuppressive effect of mu-opioids as a part of balanced anesthetic technique with inhalational agents might help to maintain cell- and cytokine-mediated immune balance in an exaggerated inflammatory response seen after cardiac surgery with the use of CBP.**
**Alpha($\alpha_2$)-Agonists: clonidine, dexmedetomidine**

**Neurohumoral response**

The $\alpha_2$-agonists clonidine and dexmedetomidine are known to reduce anesthetic requirements, to attenuate sympathoadrenal responses during surgery and to reduce the plasma concentration of norepinephrine through stimulation of presynaptic $\alpha_2$ adrenoceptors (35, 36, 37).

**Cell- and cytokine-mediated immune reactivity**

There is some evidence that $\alpha_2$-agonists affect cell-mediated immune responses (2). In addition, T cells expressed both alpha(1)-AR and alpha(2)-AR mRNAs (38). The expression of both alpha(1)-AR and alpha(2)-AR mRNAs was significantly higher in Con A-activated lymphocytes than in the resting lymphocytes. Phenylephrine, a selective alpha(1)-AR agonist, had no evident effect on lymphocyte proliferation nor on IFN-gamma and IL-4 production induced by Con A. However, the selective alpha(2)-AR agonist clonidine attenuated Con A-induced lymphocyte proliferation as well as IFN-gamma and IL-4 production. Von Dossow et al. (39) previously demonstrated that clonidine changes the T cell subset ratio six hours after cardiac surgery with the use of CPB in favor of a proinflammatory response without any immunosuppressive effect.

*In conclusion, in cardiac surgery with the use of CPB the immunosuppressive effects of inhalational anesthetics and mu-opioids are favorable regarding the exaggerated inflammatory response whereas total-intravenous anesthesia might be the preferred regimen in patients with an already altered immune response. However, the effect on outcome remains to be determined.*
References


22. Von Dossow V, Baur S, Sander M et al. Propofol increased the Interleukin-6 to interleukin-10 ratio more than isoflurane after surgery in long-term alcoholic patients. JIMR 2007; 35: 395-405


