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Perioperative cell-mediated immune response

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TABLE OF CONTENT

1. ABSTRACT

Innate and acquired immunity play a pivotal role in the host defense response. Pain, surgical stress, tissue injury and invasive micro-organisms are known to modulate complex immune responses in patients undergoing major surgery, which can lead to subsequent increased susceptibility to postoperative infections. Anesthetics may influence the immune response indirectly through modulation of the neurohumoral response or directly by acting on immune competent cells. In particular, cell-mediated immune balance seems to be affected by anesthetics and this might account for anesthetic-dependant risk of postoperative infections. Consequently, in order to fully understand the immunomodulating properties and ensuing clinical relevance of anesthetics it will be necessary to investigate each agent individually and in a variety of clinical settings. The existing research in this field, most of which is experimental, has yielded different results. The goal of further clinical studies must be to establish the immunomodulating properties of individual anesthetic agents so that selection can be tailored to the individual patient's pre-operative immune status and intraoperative course.

2. INTRODUCTION

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

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 the mediators of this type of counter-inflammatory response also have strong immunosuppressive activity (5). Consequently, clinical observations along with numerous studies in animal

models suggest that host immune response following a major surgical trauma involve various degrees of down-regulation of cellular immunity in the early postoperative period (3, 6). These phenomena may contribute to infectious complications after surgery. However, it is important to distinguish between major and minor surgery, as outlined by Kashiwabara *et al.* (7): a significant difference in the incidence of postoperative complications (systemic inflammatory response syndrome (SIRS), infections) between patients who underwent major and moderate surgery ($p < 0.039$) was demonstrated.

Recently, it has become clear that an adequate host immune response against infection is largely dependent on the activation of two functionally distinct subsets of mature CD4+ T helper cells (8, 9) which play a commanding and central role in cytokine synthesis (10). Surgery per se causes a phenotypic imbalance in the regulation of T-helper 1 (Th1) and T-helper 2 (Th2)-type immune responses (11), (see figure 1). The Th1/Th2 balance has been used to explain most of the immunological phenomena observed in autoimmune diseases, infections and tumors (12). Moreover, previous studies showed that surgical trauma induces a shift of Th1/Th2 balance towards Th2 dominance that is commensurate with the extent of trauma (13).

Several clinical and experimental studies revealed that anesthetics modify the perioperative immune stress response either indirectly (via the hypothalamic-pituitary-axis (HPA) and the sympathetic nervous system) or directly (via immune cells). Concern about the impact of anesthetic agents for general anesthesia is growing because an increasing number of patients require anesthesia. In cancer patients, immunosuppression may accelerate the growth and metastasis of cancer cells. This suggests that restriction of surgical or anesthesiological stress should be recommended (14).

Therefore, this review focuses on cell-mediated immune responses associated with major surgery. The influence of inhalational agents (isoflurane, desflurane, and sevoflurane), intravenous anesthetics (propofol), μ-opioid receptor agonists (morphine, fentanyl, sufentanil, remifentanil) and the alpha-2 agonists' clonidine and dexmedetomidine on perioperative cell-mediated immune responses will be discussed.

3. MAJOR SURGERY NEUROENDOCRINE IMMUNE RESPONSE, IMPACT OF ANESTHETICS, OPIOIDS AND ALPHA$_2$-AGONISTS

3.1. Neuroendocrine stress axis and cell-mediated immune responses after major surgery

3.1.1. Surgical setting

The response to injury, i.e. major surgery is initiated by somatic and autonomic afferent nerve impulses and the release of cytokines from the site of injury (15). The neuroendocrine 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 propiomelanocortin to adenocorticotrophin (ACTH) and ß-endorphin and their subsequent release into the systemic circulation (15, 16). 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 (16). 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. In patients after surgery cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol. A negative feedback system exists so that glucocorticoids inhibit cytokine production.

3.1.2. Non surgical setting

Hypothalamic activation of the sympathetic nervous system results in increased secretion of catecholamine from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. Norepinephrine is primarily a neurotransmitter, but there is some spillover of norepinephrine released from nerve terminals into the circulation. An interaction between the sympathetic nervous system and T cells have been described previously (17-19) (Figure 1, 20). Beta (ß) adrenoceptors are expressed on CD4+ helper and CD8+ cytotoxic cells and it is only these cells are affected by norepinephrine (NE) (17). In a recent study Swanson *et al* (18) found that exposure of naive CD4+ T cells to NE during the process of differentiation into Th1 cells caused these cells to produce higher levels of interferon-gamma (IFN-γ) than cells that had not been exposed to NE. In addition, patients with chronic heart failure receiving ß-blocker therapy exhibited significantly lower Th1/Th2 ratios, lower NE plasma levels and decreased pro-inflammatory cytokine production (19).

It is recognized that CD4 + T cells play a central role in cytokine synthesis (21, 22, 23). CD4+ cells are generally divided into two subsets: Th1 and Th2 (10). While Th1 cells regulate cell-mediated immune responses and the production of IFN- γ, Th2 cells are important in B cell proliferation and IL-4 secretion. Tissue injury induces both the innate and acquired responses (10, 22, 23). The innate immune system mounts the initial response which involves macrophages, natural killer (NK) cells and neutrophiles while the acquired immune system is induced by presentation of foreign antigens to CD4+ and CD8+ T cells. CD4+ T cell activation causes cytokine production and further amplifies the innate and acquired immune systems (24).

3.1.3. Surgery and postoperative infections

An excessive inflammatory response with alteration of cell-mediated immunity appears to be responsible for increased susceptibility to post-operative

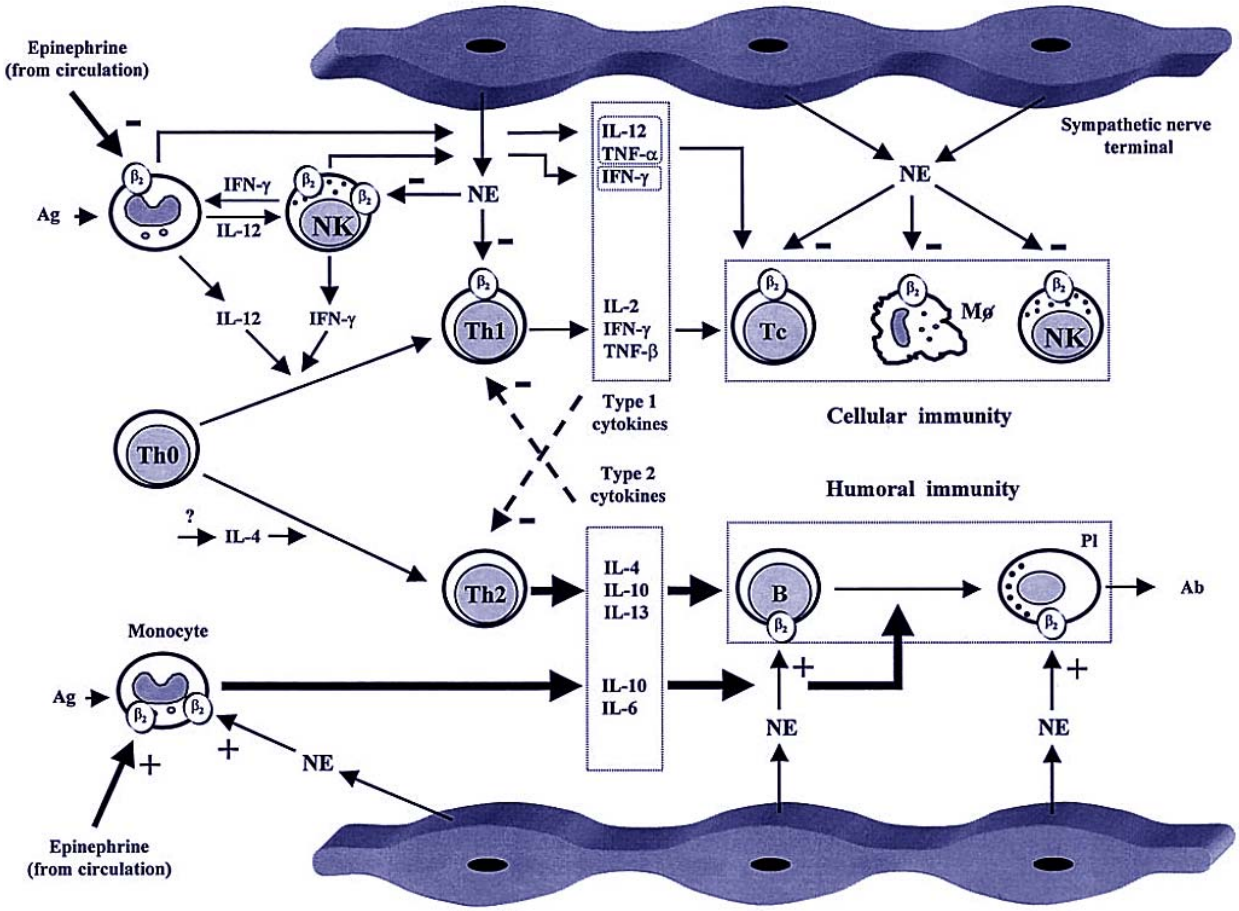

Figure 1. Role of Th1 and Th2 cells, and type 1 (proinflammatory) and type 2 (anti-inflammatory) cytokines in the regulation of cellular and humoral immunity. (20).

infection and sepsis (25). Alterations within the specific, adaptive immune system primarily affect T helper (h) cells (10, 21). The pro-inflammatory Th1 mediated pathway has been shown to be temporarily depressed while the anti-inflammatory Th2 mediated pathway is unaffected, or even disinhibited, resulting in an imbalance of the Th1/Th2 ratio after surgery (24, 26).

Indeed T cells can augment immune responses both locally and systemically, depending on the clinical setting (27, 28). An early Th1 response after surgery has been reported to support the inflammatory response by augmenting the production of the cytokines interleukin (IL)-2, IL-12 and IFN-γ after cardiac surgery and cardiopulmonary bypass (CPB) (25). The use of CPB per se induces a systemic inflammatory response syndrome with unbalanced cytokine release and subsequent prolonged activation of the immune system (29). Patients with tumor disease are known to have an impaired immune response even before surgery (22, 30): Specifically decreased IL-4 cytokine secretion by Th2 cell subsets has been demonstrated preoperatively in esophageal cancer patients (22). Furthermore, an altered and attenuated Th1/Th2 ratio prior to surgery was demonstrated in long-term alcoholic patient, which was associated with an increased postoperative infection rate (30).

3.1.4. Conclusion

Alterations of cell-mediated immune responses seem to be responsible for the increased risk of postoperative complications in patients undergoing major surgery.

3.2. Inhalational and intravenous anesthetics

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 (31-33).

3.2.1. Neuroendocrine response

Isoflurane anesthesia has been associated with higher serum concentrations of catecholamine and cortisol when compared with propofol anesthesia (32, 33) 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 (32); in cardiac patients epinephrine, norepinephrine and cortisol increased before the start of extracorporeal circulation and the increase was greater under isoflurane than propofol anesthesia (33), while in patients undergoing hysterectomy time-response curves for cortisol concentrations were steeper under isoflurane

compared with propofol anesthesia (34). This indicates that the stress response, as measured by activation of the systemic nervous system and the hypothalamic-pituitary-adrenal axis, is lower with intravenous anesthesia than with isoflurane anesthesia. However, these changes are transient and confined to brief periods during or immediately after surgery.

3.2.2. Cell-mediated immune response

It is not known whether the differing stress response between inhalational and intravenous anesthetic agents is the same in all organ systems. Furthermore, these conventional markers of stress do not provide any information on changes in the immune system and inflammatory response. Measurement of the Th1/Th2 ratio is a more useful method in this respect. Flow cytometric analysis of the proportions of CD4+ T cells producing IFN-γ and IL-4 is a functional assay that measures the ability of specific immune cells to express type 1 and type 2 cytokines after polyclonal stimulation with mitogens (35-38). Jung *et al* (36) reported that this method is sufficiently sensitive to detect IL-4 secretion in human T cell clones when cytokine inhibitors are used. In addition, the whole blood method retains T–helper lymphocytes in a microenvironment similar to that *in vivo* and is thus more suitable for studies to transport the blood samples from the field to the laboratory (37). Furthermore, flow cytometry makes it possible to analyze which lymphocyte subset is affected by major surgery (38). In contrast, numerous cytokine assays are available such as ELISA, and immunhistochemistry. One limitation of ELISA is that it does not identify the cellular source of secreted cytokines into plasma and serum (35).

Inada *et al.* (39) 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 (40) supported the findings of Inada *et al.* (39). Propofol significantly increased the IFN-γ/IL-4 ratio which reflected changes in theTh1/Th2 balance ($p < 0.01$) (40). However, a limitation of the study by Inada *et al* (39) is that they did not report the post-operative infection rate. In most clinical trials the low rate of infectious complications precludes accurate estimation of the influence of immune perturbation on the infection rate.

3.2.3. Plasma cytokines

Previous clinical studies have reported conflicting results with respect to pro- and anti-inflammatory cytokine plasma levels in patients undergoing surgery under different inhalational and intravenous anesthetic agents (31). Crozier *et al.* (31) reported lower levels of circulating IL-6 in patients receiving propofol compared to a control group receiving inhalational anesthesia. In contrast, Taylor *et al* (35) reported that supplementation with inhalational anesthesia failed to affect IL-6 response to surgery. A significant increase in circulating IL-6 and IL-10 levels under propofol compared to inhalational anesthesia has also been observed (34, 41). Gilliland *et al.* (41) showed significantly higher IL-10 levels in patients whose anesthesia was maintained with propofol. However, in the perioperative setting it is difficult to distinguish between the changes caused by surgical trauma or by anesthetic drugs. IL-6 is increased after surgery, trauma, and infection (42, 43). The immediate postoperative period is characterized by a proinflammatory response with high levels of IL-1, IL-6, TNF-alpha and activation of neutrophiles. This response and especially the postoperative level of IL-6 seem to be a measure for tissue damage (42, 43). Therefore, separation of pro- and anti-inflammatory cytokines might not provide an adequate reflection of post-operative immune balance. In addition, data obtained in clinical studies measuring release of cytokines into plasma as a result of surgery and/or anesthesia are difficult to interpret with respect to their effects on immune competent cells due to the presence of a large number of confounding variables such as depth of anesthesia and side effects of anesthetics (e.g. systemic hypotension) as well as surgical effects.

In a previous study by Sander *et al.* (44) a significant suppression of the IL-6/IL-10 ratio immediately after surgery was seen in long-term alcoholics undergoing elective surgery for resection of the upper digestive tract. Coincident with the immune alterations, these patients had a prolonged intensive care unit (ICU) stay ($P < 0.01$) and a three-fold increased rate of wound infections ($P < 0.05$) and pneumonia ($P < 0.01$). Irwin *et al.* (45) described, in a recent publication, how the IL-6/IL-10 ratio in long-term alcoholic patients was significantly decreased compared with non-alcoholic controls in *ex vivo*-stimulated lymphocytes.

In a previous study of our study-group propofol anesthesia caused an increased IL-6/IL-10 ratio on day one after surgery compared to isoflurane anesthesia in long-term alcoholic patients (46).

3.2.4. Conclusion

Perioperative immune balance is better maintained with propofol compared to inhalational anesthetics in patients undergoing major surgery. Therefore total-intravenous anesthesia might be the preferred regimen in patients with an already altered immune response. The effect on outcome remains to be determined**.**

3.3. Opioids

3.3.1. Neuroendocrine response

It is long established that opioids suppress hypothalamic and pituitary hormone secretion (47). Morphine suppresses the release of corticotrophin and consequently cortisol under both normal and stress conditions resulting in hypothalamic inhibition (48). The effects of morphine and other opioids have been especially well documented in cardiac surgery (48). 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 (48). 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 (16).

3.3.2. Cell-mediated immune response

Apart from their neuro-humoral effects, opioids also exert an effect on the immune system by modulating cytokine response either via opioid receptors on immune cells or via opioid receptors within the central nervous system (49-52). Modulation by μ-agonists has been demonstrated previously in a range of immune cells including macrophages, monocytes, NK cells and T cells (50, 52). Short-term in-vivo exposure to fentanyl increases NK cytotoxicity but does not affect the T-lymphocyte proliferation response in healthy volunteers (53). Continuous infusion of remifentanil (0.02-0.04 μg/kg/min) does not affect NK cell number in healthy volunteers (54). In animal studies the effects of opioids on NK cell activity can be investigated more fully (55, 56). Twenty-four hours of fentanyl administration significantly decreased NK cytotoxicity as well as IFN-γ and IL-2 release upon Con A stimulation whereas buprenorphine in contrast affected neither NK cytotoxicity nor cytokine release upon Con-A stimulation (55). It has been hypothesized that the immunomodulating properties of opioids may be mediated via the μ-opioid receptor. As buprenorphine is a partial μ-agonist, this might explain the different effects mentioned above. Sacerdote *et al.* (56) demonstrated that continuous remifentanil infusion (0.1μg $kg^{-1}min^{-1}$) suppresses NK cytotoxicity and decreases splenocyte proliferation for up to five hours after end of infusion.

3.3.3. Plasma cytokines

Brix-Christensen (57) showed an immediate down-regulation of HLA-DR with fentanyl-based analgesia as well as a simultaneous pro- and anti-inflammatory cytokine response until day three after cardiac surgery. Liu *et al.* (58) demonstrated significantly lower pro-inflammatory response (TNF-α and IL-6) with high-dose fentanyl (60 μg kg^{-1} and 100 μg kg^{-1}) compared to low-dose fentanyl (30 μg kg^{-1}) in patients undergoing valve replacement two hours after removal of aortic clamp. One limitation of these studies is that they analyzed plasma cytokines involved in the systemic inflammatory response. As early T cell activation has been hypothesized to reflect the extent of initial inflammation, the cell-mediated immune response should also be addressed in perioperative studies. T cell function, monocyte function and HLA-DR expression on monocytes are particularly important in the early postoperative period. As monocyte function and HLD-DR expression decrease both during and after surgery, it follows that T cell mediated immunity plays a pivotal role in maintaining immune balance after surgery.

3.3.4. Conclusion

The influence of opioids on perioperative cell-mediated immune responses is still unclear and remains to be characterized.

3.4. Alpha-2 agonists: clonidine and dexmedetomidine

3.4.1. Neuroendocrine response

The alpha $(\alpha)_2$-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 α_2 adrenoceptors (59, 60). While the use of clonidine during surgery does not appear to influence the perioperative stress response, as measured by ACTH and cortisol plasma levels (61), the use of intraoperative dexmedetomidine attenuated significantly plasma cortisol, epinephrine, norepinephrine, and blood glucose levels in pediatric patients undergoing corrective surgery for congenital heart disease ($p < 0.05$). However, dexmedetomidine used for sedation in the intensive care unit did not influence adrenal steroid genesis (62).

3.4.2. Cell-mediated immune response

There is some evidence that alpha (α) 2-agonists affect cell-mediated immune responses (63-65). Our study-group (63) has previously demonstrated that clonidine changes the T cell subset ratio six hours after surgery in favor of a pro-inflammatory response. This change is in favor of cell-mediated immunity as the augmentation of CD4+ (Th) cells is greater than that of CD8+ (Tc) cells (38). The Th1 cells may support an inflammatory response by producing the cytokines IL-2, IL-12 and IFN-γ (64). In addition, it has been hypothesized that this early T-cell response might reflect the magnitude and nature of the immunoinflammation (65). In accordance to our results Inada *et al* (66) demonstrated that subhypnotic doses of dexmedetomidine decreased the ratio of helper T lymphocytes subsets, Th1 to Th2 (Th1/Th2) in the spleen. In contrast Ellis *et al.* (67) were unable to demonstrate any changes in lymphocyte subsets with clonidine. They were however able confirm earlier reports that NE plasma levels are significantly decreased in patients undergoing major non-cardiac surgery (60, 67, 68). Dorman *et al.* (60) noted that the major effect of α_2 –adrenergic receptor agonists is on tonic activity while SNS responsivity to stressful stimuli appears to be unaffected.

The influence of the sympathetic nerve system on the immune system, in particular the cell-mediated immune system, is not fully understood (69, 70). A previous study (70) presented evidence that catecholamines may be pivotal in the modulation of Th1 and Th2 cell interactions. Interestingly, ß-adrenoreceptors (AR) have been documented on CD4+ and CD8+ T cells (70). Specifically they are expressed on naive CD4+ helper T cells but not on Th2 cells. ß-AR activation on T-cells results in cytokine production (70). Swanson *et al.* (18) found that exposure of naive CD4+ T cells to NE during the process of differentiation into Th1 cells caused these cells to produce higher levels of IFN-γ following antigen stimulation than cells that had not been exposed to norepinephrine. In

addition, ß-blocker therapy caused significant lower Th1/Th2 ratios and decreased norepinephrine levels as well as lower IFN-γ levels in patients with chronic heart failure (19). In particular, in sepsis, impairment of the intestinal microcirculation has been recognized as an important factor in the pathogenesis of endotoxin related sepsis syndrome. Birnbaum *et al.* (71) investigated the effects of endotoxemia on the variability of intestinal microvascular blood flow (IMBF) and arterial blood pressure in a prospective, randomized, controlled animal study. Clonidine administration attenuated the IMBF decrease and significantly diminished the increase in LF spectral power of IMBF and blood pressure. This means, that endotoxemia is associated with increased sympathetic outflow to the systemic vasculature, which can be attenuated by clonidine.

3.4.3. Conclusion

The immunomodulating effects of clonidine seem to be limited to T-cell-mediated immune responses. The effect is via a reduction in sympathetic tone which might be favorable with respect to the immune balance as the alteration of cell-mediated immune response following major surgery appears to be responsible for the increased susceptibility of infections. However, future studies are needed to clarify the immunomodulatory effects of alpha2-agonists, its influence on the perioperative immune balance and their clinical relevance.

4. SUMMARY AND PERSPECTIVE

Based on controversially discussed in-vitro and *in vivo* studies regarding the influence of anesthetics, opioids and alpha-agonists on cell-mediated immune responses regarding the clinical relevance it seems that the Th1/Th2 ratio as well as pro- and anti-inflammatory cytokine ratios might be appropriate parameters presenting perioperative immune balance, especially in immunocompromised patients undergoing major surgery. Therefore, further future studies are necessary to investigate each anesthetic substance in different patient collective (i.e. patients with pre-existing immune perturbations (tumor patients, chronic alcohol abuse, cardiopulmonary diseases) regarding the clinical significance and postoperative infection rate. This might help to choose the appropriate anesthesiological management**.**

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Abbreviations: SIRS: systemic inflammatory response syndrome, Th1/Th2: T-helper 1/2 cells, HPA: hypothalamic-pituitary-axis, ACTH. adenocorticotrophin, NE: norepinephrine, CPB: cardiopulmonary bypass, ICU: intensive care unit, IFN-g: interferon-gamma, IL: interleukin, ß-(AR): beta-adrenoreceptors, IMBF: intestinal microvascular blood flow

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