

Immunomodulatory effects of anesthetics in obese patients

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Abstract

Anesthesia and surgery have an impact on inflammatory responses, which influences perioperative homeostasis. Inhalational and intravenous anesthesia can alter immune-system homeostasis through multiple processes that include activation of immune cells (such as monocytes, neutrophils, and specific tissue macrophages) with release of pro- or anti-inflammatory interleukins, upregulation of cell adhesion molecules, and overproduction of oxidative radicals. The response depends on the timing of anesthesia, anesthetic agents used, and mechanisms involved in the development of inflammation or immunosuppression. Obese patients are at increased risk for chronic diseases and may have the metabolic syndrome, which features insulin resistance and chronic low-grade inflammation. Evidence has shown that obesity has adverse impacts on surgical outcome, and that immune cells play an important role in this process. Understanding the effects of anesthetics on immune-system cells in obese patients is important to support proper selection of anesthetic agents, which may affect postoperative outcomes. This review article aims to integrate current knowledge regarding the effects of commonly used anesthetic agents on the lungs and immune response with the underlying immunology of obesity. Additionally, it identifies knowledge gaps for future research to guide optimal selection of anesthetic agents for obese patients from an immunomodulatory standpoint.

Key words: Anesthesia; Immune system; Perioperative care; Obesity; Inflammation

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Core tip: Anesthetic agents have been studied not only for their effects on anesthesia and analgesia, but also their action on the lungs and immune system. Obesity is associated with a chronic state of low-grade systemic inflammation, and may predispose to development of comorbidities. Although efforts have been made to develop guidelines for anesthesia in obesity, to date, no ideal drug combination has been found. Optimization of the immunomodulatory properties of anesthetic agents may enable perioperative modulation of inflammatory response in obese patients and improve postoperative outcomes.

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INTRODUCTION

Obesity and associated comorbidities are increasing at epidemic proportions globally^[1], with a substantial impact on postoperative outcomes for affected individuals undergoing minor or major surgical procedures that require anesthesia. Intravenous and inhalational anesthetics (IAs) have been shown to modulate the innate and adaptive immune responses, as well as indirect effectors of immunity^[2,3].

Since obesity results in chronic low-grade inflammation or meta-inflammation^[4] associated with increased circulating proinflammatory factors, it has been proposed that anesthetic agents may modulate the already altered immune function in obesity, with particular emphasis on pulmonary inflammation.

This review article aims to integrate current knowledge regarding the effects of commonly used anesthetic agents on the lungs and immune response with the underlying immunology of obesity. Additionally, it provides insights and future perspectives into the safe use of anesthetics as immunomodulators for obese patients. Better knowledge of the impact of anesthetic agents on the immune system, especially in the setting of obesity, may improve perioperative management and outcome.

IMMUNE AND INFLAMMATORY CHANGES DUE TO OBESITY: THE ROLE OF IMMUNE CELL INFILTRATION IN ADIPOSE TISSUE

Healthy adipose tissue (AT) is composed of a type-2 polarized immune system, which maintains AT macro-

phages (ATM) in an M2-like (pro-resolution) state. While in this form, AT is mainly composed of eosinophils, invariant-chain natural killer T (iNKT) cells^[5], and regulatory T (Treg) cells^[6], which produce interleukin (IL)-4, IL-13, and IL-10. Adipocytes also contribute to the type 2 immune response through production of adiponectin, which exhibits a strong anti-inflammatory effect^[7]. These type 2 immune cells are supported by a stromal structure, which promotes immune cell viability through the production of several cytokines, with IL-33 playing a particularly important role^[8,9]. Moreover, in order to sustain this environment, AT cells engage in extensive cross-talk to (re)model AT structure and phenotype^[10].

The early phases of the diet-induced obesity (DIO) period are characterized by an increase in the amount of fat per adipocyte and an accumulation of immune cells. Acute changes in the microenvironment, such as alterations in oxygen supply and consumption, contribute to triggering a rapid increase in the number of neutrophils^[11]. Adipocytes become hypertrophic and hyperplastic. This is associated with a shift in adipokine production from adiponectin to leptin, monocyte chemo-attractant protein-1 (MCP-1), and IL-6, as well as resistin, visfatin, tumor necrosis factor (TNF)- α , retinol binding protein 4 (RBP4), lipocalin-2, and CXCL5^[12]. Leptin directly increase the production of several proinflammatory cytokines, such as IL-6, TNF- α , the chemokines CCL2/MCP-1, and leukotriene B₄ (LTB₄) in peripheral blood monocytes and resident tissue macrophages^[13]. Leptin can also induce the production of reactive intermediates in macrophages, neutrophils, and endothelial cells, as well as potentiate interferon (IFN)- γ induced expression of nitric oxide (NO) synthase^[14-16], whereas adiponectin, IL-10, and omentin, which have anti-inflammatory effects, are downregulated^[17]. In addition, innate inflammatory molecules such as acute phase reactants, C-reactive protein (CRP)^[18], complement components C2, C3, and C4^[19,20], and other immune-modulating mediators produced in AT contribute to the intricate connection between fat and its tissue-resident immune cells.

The adaptive immunity role is mediated by T-lymphocyte infiltration during early AT inflammation, preceding macrophage recruitment^[21,22]. Most of these are CD4⁺ lymphocytes that differentiate to TH1-cells, governing the local inflammatory process through the release of proinflammatory cytokines like IFN- γ and TNF- α . T-cell recruitment is usually mediated by chemokines released from endothelial cells, stromal cells, or macrophages. While, on the one hand, T-cell derived IFN- γ promotes the recruitment of monocytes by MCP-1 secretion from preadipocytes, it also activates other cells, including macrophages^[21].

Resident and recruited ATM are the most common immune cell types in AT, and their infiltration is associated with AT inflammation^[23,24]. Recruited AT macrophages induce tissue inflammation when their

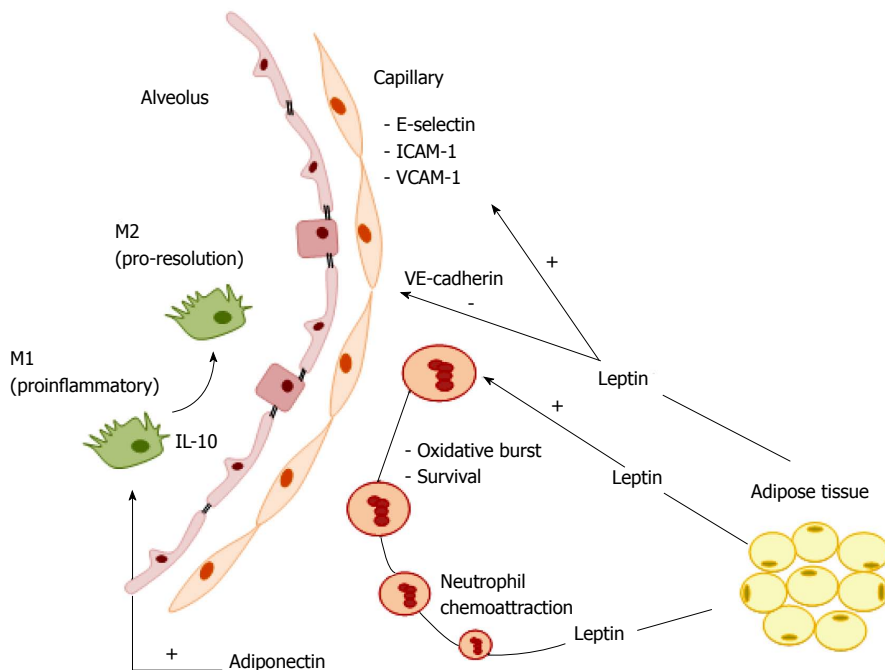


Figure 1 Model of obesity-associated pulmonary inflammation. Lung immune cells and inflammation due to obesity. Leptin is implicated in inflammatory respiratory diseases as a neutrophil chemoattractant. The association between obesity and LPS-induced lung inflammation involves an increase in monocytes and lymphocytes, as well as in intracellular adhesion molecule (ICAM)-1 expression in alveolar macrophages, suggesting their polarization toward a pro-inflammatory M1 phenotype. Obesity impairs vascular homeostasis, facilitating increased susceptibility to inflammatory lung vascular diseases by affecting structural cells in the alveolar-capillary membrane. The lung endothelium of obese mice has been shown to express higher levels of leukocyte adhesion markers (E-selectin, ICAM-1, VCAM-1) and lower levels of junctional proteins (VE-cadherin and β -catenin). Adiponectin has anti-inflammatory properties, mainly by its effects on toll-like receptor (TLR) pathway-mediated NF- κ B signaling, which regulates the shift from M1 to M2 macrophage polarization, and suppresses differentiation of M1 macrophages by downregulating the pro-inflammatory cytokines TNF- α , MCP-1, and IL-6. Adiponectin also promotes expression of the anti-inflammatory factor IL-10 in macrophages via cAMP-dependent mechanisms. TNF: Tumor necrosis factor; IL: Interleukin; LPS: Lipopolysaccharide.

polarization shifts from an M2 type to an activated proinflammatory M1 state. Stimuli for this shift toward the M1 phenotype includes systemic factors, such as increase in free fatty acids (FFAs), which stimulates toll-like receptors (TLR)-4 on macrophages^[25], and activation of the inflammasome, which is responsible for production of the proinflammatory cytokines IL-1 β and IL-18^[26]. In addition, IFN- γ is a potent local inducer of M1 polarization during ATM inflammation^[27].

The link between metabolism and immunity at the intracellular level occurs through activation of nuclear factor- κ B (NF- κ B) and its cytoplasmic inhibitor I κ B. Likewise, other inflammatory factors, such as c-Jun N-terminal protein kinases (JNK), are activated^[28,29]. These proinflammatory mediators are produced in excess, spilling into the peripheral circulation and contributing to the low-grade systemic inflammation that ultimately influences the development of obesity-associated comorbidities, including the pulmonary immune response, thus contributing to pulmonary inflammation^[12,30].

AT immune cells contribute to the maintenance of homeostasis and development of chronic inflammation and are responsible for the mechanisms underlying obesity-associated complications and impairment of normal immune system functioning, thus further perpetuating chronic disease development and metabolic

complications.

LUNG IMMUNE CELLS AND OBESITY-ASSOCIATED INFLAMMATION

Several mediators elicited by obesity alter immune and inflammatory responses in the lung, and may induce obesity-associated changes to adipokines and lung immune cells.

Leptin

Several lung cell types, such as leukocytes, airway smooth muscle cells, alveolar epithelial cells, and macrophages, express the functional leptin receptor, which, when bound to its main ligand (systemic leptin), participates in triggering inflammatory respiratory diseases. Lungs represent a target organ for leptin signaling. In this line, leptin stimulates neutrophil and macrophage release of cytokines (TNF- α , IL-6, IL-12), eicosanoids, and NO and induces neutrophil oxidative burst^[31]. Endogenous leptin has two main effects in the lungs (Figure 1). First, it acts as a neutrophil chemoattractant to the lungs^[32]. Once neutrophil levels are increased, leptin lengthens neutrophil survival by delaying or inhibiting apoptosis^[33]. Additionally, obese patients with increased levels of leptin exhibited increased susceptibility to respiratory infections, in an association that may be independent and

likely additive to metabolic syndrome-related factors^[34]. Furthermore, the proinflammatory effects of leptin may contribute to a higher incidence of asthma in the obese population^[35]. In chronic obstructive pulmonary disease^[36,37], the higher the leptin production, the greater the severity of the disease^[38,39]. In the setting of obesity, not only immune cells but also structural cells in the alveolar-capillary membrane are altered. In obese mice, the lung endothelium was found to express higher levels of leukocyte adhesion markers (E-selectin, ICAM-1 and VCAM-1) and lower levels of junctional proteins (VE-cadherin and β -catenin) (Figure 1), providing further evidence that obesity may impair vascular homeostasis and increase susceptibility to inflammatory lung vascular diseases^[40].

In short, leptin plays an important role in respiratory immune responses and pathogenesis of inflammatory respiratory conditions by acting on different cell types in the lung.

Adiponectin

Adiponectin is a well-defined obesity marker that has anti-inflammatory properties. Its predominant immune-related functions involve suppression of inflammation by clearance of apoptotic cell debris^[41] and promotion of an anti-inflammatory phenotype in the lung by blunting oxidative stress, inflammation, and angiogenesis. However, several of these immune-related functions depend on the respective adiponectin receptor. AdipoR1, AdipoR2, T-cadherin, and calreticulin are detected in several lung cells^[42]. The structure of adiponectin resembles those of complement factor C1q and of surfactant proteins, which act as pattern recognition molecules limiting lung inflammation^[43]. Adiponectin receptors are also involved in the regulation of macrophage proliferation and function. AdipoR1 mediates adiponectin suppression of NF- κ B activation and proinflammatory cytokine expression in macrophages^[44,45], AdipoR2 is involved in adiponectin-mediated M2 polarization^[46], and T-cadherin has been shown to play an essential role in the stimulatory effects of adiponectin on M2 macrophage proliferation^[47]. The anti-inflammatory effects of adiponectin are mainly guided by the toll-like receptor (TLR) mediated NF- κ B signaling pathway, which modulates a shift in macrophage polarization from M1 to M2 (Figure 1) and suppresses differentiation of M1 macrophages by downregulating the proinflammatory cytokines TNF- α , MCP-1, and IL-6^[48,49]. Moreover, adiponectin increases expression of the anti-inflammatory factor IL-10 in macrophages *via* cAMP-dependent mechanisms^[50]. Adiponectin has also been proposed to regulate energy and metabolism by targeting innate-like lymphocytes (ILC2)^[10,51], natural killer T (NKT)^[52], and gamma delta T ($\gamma\delta$ T) cells^[53].

Adiponectin senses metabolic stress and modulates metabolic adaptation by targeting functions of the innate immune system, including macrophage polarization and lymphocyte activity.

ANESTHESIA, ANESTHETICS, AND IMMUNOMODULATION

Anesthesia and the surgical stress response result in several immunological alterations, which cannot be easily separated. The pharmacological effects of anesthetic drugs (sedation, anesthesia, and analgesia) have been widely studied, as have their actions on several cell types, including inflammatory cells, by altering cytokine release^[54]; cytokine receptor expression^[55]; phagocytosis or cytotoxic actions^[56]; and transcription or translation of protein mediators^[57,58]. Depending on the clinical setting, immunosuppression and activation can be either detrimental or beneficial. These effects are clinically important because the balance between pro- and anti-inflammatory cytokine secretion is associated with surgical outcomes.

Immune cells are categorized into two lines according to their maturation site: The myeloid lineage, which includes macrophages, dendritic cells (DCs), mast cells, and granulocytes (neutrophils, eosinophils and basophils); and the lymphoid lineage, which is composed of T and B lymphocytes, natural killer (NK) cells, and NK T cells^[59,60]. Myeloid cells are considered the main players in innate immunity, and play important roles in adaptive immunity as well; they serve as antigen presenters and macrophages, mast cells, and neutrophils produce several cytokines, thus activating T and B lymphocytes^[60]. Immunomodulation can have a dichotomous sense whereby suppression of the immune response can prevent further injury, as observed in models of acute inflammation^[61], but also prevent the body from counteracting infections and increase the risk of opportunistic infections. In these scenarios, both inhalational and intravenous anesthetic agents may jeopardize or improve immune function.

IA agents

The action of IAs on immune cells has been extensively reviewed in preclinical studies^[2,62,63]. *In vitro* experiments on immune cells revealed generally transient, dose- and time-dependent effects predominantly on neutrophil function^[64-66], lymphocyte proliferation^[67], suppression of inflammatory cytokines in rat alveolar cells, and decrease in the expression of inducible NO synthase by inhibition of voltage-dependent calcium channels, reducing intracellular calcium concentrations^[68]. However, in an ischemic setting, the suppression of neutrophil adhesion had a positive effect against the deleterious effects of polymorphonuclear cells, improving cardiac function^[69-72]. Furthermore, exposure to the isoflurane attenuated villus, hepatic, and renal injuries in a mouse model of intestinal ischemia; these effects were mediated *via* plasma membrane phosphatidylserine externalization and subsequent release of the anti-inflammatory and anti-apoptotic cytokine transforming growth factor β 1 (TGF- β 1)^[73]. In both studies, the proposed mechanisms for protection rely on modulation

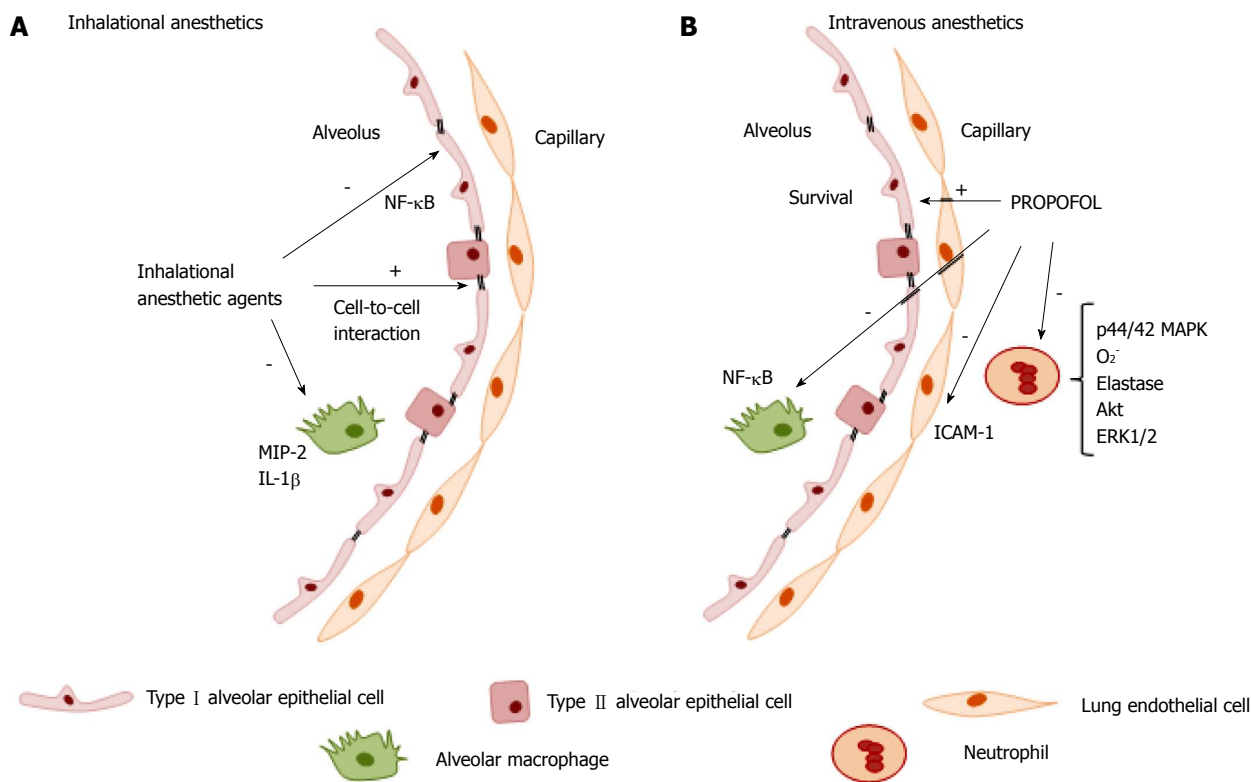


Figure 2 Modulatory effects of anesthetic agents on lung immune cells. A: Inhaled anesthetics: Decreased neutrophil influx, synthesis, and expression of macrophage inflammatory protein (MIP)-2, IL-1 β , and stress proteins heme oxygenase (HO-1) and heat shock protein (HSP-70). Reduction of pro-inflammatory cytokine release, inhibition of iNOS expression and activity by blockade of NF- κ B activation in lung tissue, inhibition of proapoptotic procaspase protein expression, and maintenance of alveolar epithelial adherence by attenuating reduction of zona occludens 1 (ZO-1) levels; B: Intravenous anesthetic (propofol): Impairs neutrophil activity by inhibition of phosphorylation of the mitogen-activated protein kinases p44/42 MAPK signaling pathway and disrupts the downstream signaling pathway involving calcium, Akt, and ERK1/2, which decreases superoxide generation, elastase release, and chemotaxis.

of endothelial and neutrophil adhesion molecules and reduction of neutrophil migration and margination into tissues^[74]. In human endothelial cells, the effects of isoflurane against TNF- α -induced apoptosis are mediated by the phosphorylation of extracellular signal-regulated kinase (ERK MAPK) and induction of sphingosine kinase 1 (SK1) to increase production of the lysophospholipid S1P, a cytoprotective signaling molecule product of sphingomyelin hydrolysis that functions as an extracellular ligand for specific G protein-coupled receptors and as an intracellular second messenger^[75]. In the context of acute inflammatory lung injury (Figure 2A), isoflurane has been shown to decrease neutrophil influx, as well as the synthesis and expression of macrophage inflammatory protein (MIP)-2, IL-1 β , and the stress proteins heme oxygenase (HO-1) and heat shock protein (HSP-70)^[76-79]. These studies showed reduction of proinflammatory cytokine release through several mechanisms: (1) inhibition of NF- κ B translocation into the nuclei of human epithelial cells^[58,76]; (2) inhibition of inducible nitric oxide synthase (iNOS) expression and blockade of NF- κ B activation in a mouse model of lung injury; (3) inhibition of proapoptotic procaspase-8, procaspase-3, and inactivated proapoptotic protein Bax expression; (4) promotion of phosphatidylinositol-3-kinase/Akt activation and enhanced expression of the antiapoptotic B-cell

lymphoma-2 (Bcl-2)-related protein homeostasis^[80]; and (5) maintenance of alveolar epithelial adherence by attenuating reduction of zona occludens 1 (ZO-1) levels^[81].

Intravenous anesthetic agents

The intravenous anesthetics (IVAs) ketamine and dexmedetomidine, although very important in clinical practice, have well-recognized and characterized immunomodulatory effects and will not be covered in the present review. The immunomodulatory effects of propofol have been investigated since it is widely used for general anesthesia and for sedation at sub-anesthetic doses. *In vitro* studies have shown that use of propofol at clinically relevant plasma concentrations impairs several monocyte and neutrophil functions, such as chemotaxis^[82,83], phagocytosis^[84], respiratory oxidative burst activity^[85] cellular killing processes, and bacterial clearance^[56,86] (Figure 2B). Some of these inhibitory properties are related to its lipid vehicle^[87]. However, at the intracellular signal transduction level, Nagata *et al*^[88] have proposed that some of the inhibitory effects of propofol on neutrophil activity may be mediated by inhibition of the phosphorylation of the mitogen-activated protein kinases p44/42 MAPK signaling pathway. A role of other pathways (such as p38 MAPK) in neutrophil chemotaxis has also been posited. Recently, Yang *et al*^[89]

proposed a novel mechanism for the anti-inflammatory effects of propofol on fMLF-activated human neutrophils. Propofol decreased superoxide generation, elastase release, and chemotaxis, in a mechanism mediated by competitive blockade of the interaction between fMLF and its formyl peptide receptor (FPR)1, thus disrupting the downstream signaling pathway involving calcium, Akt, and ERK1/2. This provides additional evidence of the potential therapeutic effect of propofol to attenuate neutrophil-mediated inflammatory diseases^[89]. In an animal model of endotoxemia, the anti-inflammatory effect of propofol decreased TNF- α , IL-1, and IL-6 levels^[90]. Further research in murine macrophages suggests that propofol suppresses lipopolysaccharide (LPS)/TLR4-mediated inflammation through inhibition of NF- κ B activation^[91] and does not affect MAPKs, including ERK1/2, p38 MAPK, or JNK. The antioxidant properties of propofol, capable of regulating reactive oxygen species (ROS)-mediated Akt and NF- κ B signaling, have also been considered. In a clinical study of patients undergoing craniotomy, propofol prevented the decrease in Th1/Th2 cell ratio seen with isoflurane anesthesia^[92]. However, no differences in neutrophil function or cellular markers in lymphocytes and monocytes have been observed in patients with severe brain injury requiring long-term sedation with propofol^[93].

Studies have demonstrated several effects of propofol in the pulmonary immune response to acute inflammation. It protected cultured alveolar epithelial cells from apoptosis and autophagy by prevention of LPS-induced mitochondrial dysfunction and inhibition of LPS-induced activation of apoptotic signals (caspase 9 activity, ROS overproduction, and Ca²⁺ accumulation)^[94,95]; attenuated iNOS mRNA expression, NO, and TNF- α , which was associated with improved survival in a murine model of endotoxin-induced acute lung injury^[94]; decreased neutrophil influx into the lungs through reduction of ICAM-1 expression^[96]; reduced apoptosis of lung epithelial cells by downregulation of LPS-induced cytokines (IL-6, IL-8, TNF- α); and reduced levels of hypoxia-inducible factor (HIF)-1 α , a transcription factor essential for regulating oxygen homeostasis^[97]. The lipid carrier vehicle or other constituents of propofol formulations may also contribute to these immunomodulatory effects^[87,98].

Many IVAs, including propofol, barbiturates, and benzodiazepines, produce their sedative and anesthetic effects on the central nervous system by inhibition of the GABA_A receptor^[99]. It is also known that immune system cells are capable of synthesizing and releasing GABA neurotransmitters, which are parts of the neuronal GABA signaling system. The absence of a presynaptic terminal defines these channels in immune cells as extrasynaptic-like channels^[100]. GABA_A receptors are present on immune cells, and are a potential site of drug action^[101]. Studies have shown that, in asthmatic mice, the anti-inflammatory effect of propofol on Th2 inflammation is mediated by inhibition of Th2 cell differentiation, a mechanism attributed to

induction of apoptosis *via* the GABA receptor during Th2 development^[102].

In contrast, impairment of immune function by anesthetics may play a role in immunocompromised patients. In this line, Wheeler *et al.*^[103] demonstrated that, through their actions on the GABA_A receptor, propofol and thiopental inhibited monocyte chemotaxis and phagocytosis. The implications clinically proposed reflect this dichotomous sense: If a patient's primary pathology is inflammatory, the immunomodulatory effects of propofol or thiopental could be therapeutic, but if the immune response is ineffective, these agents may increase the risk of infection^[103].

Opioids

Although the main role of opioid peptides is the modulation of pain by binding to the opioid receptors widely distributed in the central nervous system, there is evidence of immunomodulatory effects exerted by endogenous and synthetic peptides, which activate opioid receptors. Different opioids show different effects on the immune system; immunosuppressive, immunostimulatory, or dual. Proposed mechanisms and sites of action of opioid-mediated immune modulation include: (1) direct action on the immune cells to modulate immune response, with the mu opioid receptor as the main molecular target; (2) the hypothalamic-pituitary-adrenal axis (HPA); and (3) modulation of the sympathetic activity, either in isolation or a combination thereof^[104]. The interaction of opioids with each of these sites is complex and both species- and time-dependent. Regarding T helper cell balance, some opioids (fentanyl, methadone) have been shown to induce IL-4 and exert an anti-inflammatory effect on human T lymphocytes. Conversely, morphine and buprenorphine have not been shown to increase IL-4 mRNA or protein levels^[105]. The proposed mechanism of this effect is that different agonists at opioid receptors in T cells may induce different signaling pathways or activate certain pathways with differential intensity.

Chronic morphine administration can suppress the innate immune system by inhibiting cytokine secretion, decreasing bacterial clearance by inhibiting macrophage phagocytosis, and altering leukocyte recruitment^[106,107]. On the adaptive immune system, morphine interferes with antigen presentation, prevents activation and proliferation of T lymphocytes, and decreases T cell responses, contributing to lymphocyte apoptosis and B cell differentiation into antibody-secreting plasma cells^[106,108]. Therefore, morphine use may be advantageous early in the inflammatory process, but after the initial inflammatory stage, its administration might be associated with an increase rate of infection^[106].

While many experimental studies have highlighted the significant immunosuppression caused by opioids or their withdrawal^[109], the results from clinical studies are still vague. No conclusive evidence exists that opioids contribute to or prevent infections perioperatively, in the

Table 1 Clinical studies of effects of anesthesia on immune cells and outcomes in obese patients

Ref.	Population	Interventions	Comparison	Outcome
Abramo <i>et al</i> ^[120]	Morbidly obese patients undergoing laparoscopic gastric bypass (<i>n</i> = 30)	TIVA Sevoflurane anesthesia Xenon anesthesia	Serum levels of IL-6, IL-10, TNF- α , and NO before anesthesia, at the end of surgery, and 12 h after the end of surgery	At the end of surgery, IL-10 and TNF- α levels were lower in patients anesthetized with xenon than in those given sevoflurane or TIVA
Roussabrov <i>et al</i> ^[121]	Obese patients undergoing short-duration gastric or uterine surgery (<i>n</i> = 36)	Ketamine (IV) pre-induction compared with no ketamine before general anesthesia	Serum levels of IL-1 β , IL-2, IL-6, TNF- α , lymphocyte proliferation, and NK cell cytotoxicity	Results to those of previous studies in lean patients: No change in inflammation or immune response (11 studies), suppressed immune response (9 studies), or enhanced immune responses (1 study)

Summary of results from clinical studies comparing inhalational and intravenous anesthetics according to population, intervention, comparison, and outcomes. IV: Intravenous; IL: Interleukin; TNF: Tumor necrosis factor; NK: Natural killer cells; NO: Nitric oxide; TIVA: Total intravenous anesthesia.

ICU, or when used in the treatment of acute or chronic pain. Moreover, coexisting or underlying diseases such as cancer, diabetes mellitus, sepsis, and even obesity can all induce significant alterations in immune status. These comorbidities and some medications often used concomitantly in the perioperative period, such as corticosteroids, might modify the potential role of opioid-induced immunosuppression^[110].

IAs and IVAs have diverse immunomodulatory effects that may yield positive or negative consequences on different disease processes (such as endotoxemia, generalized sepsis, tumor growth and metastasis, and ischemia-reperfusion injury). Therefore, anesthesiologists should consider the immunomodulatory effects of anesthetic drugs when designing anesthetic protocols for their patients. Considering the influence of obesity and anesthetic agents on lung immune cells, it is important to investigate the possible joint role of these factors, *e.g.*, during anesthesia induction in the obese population.

IMMUNOMODULATORY EFFECTS OF ANESTHETICS IN OBESITY

Obesity is a heterogenous condition. Inter-individual variability in AT distribution, presence of the metabolic syndrome, and other associated comorbidities confer several degrees of risk and require different levels of care, thus creating potential confounders that may affect outcomes in research studies. Therefore, perioperative care and anesthesia in obese patients are a great challenge. To date, several studies have proposed to answer the question of which anesthetic agent is best for the obese patient^[111-114]. Most of these investigations have evaluated primary outcomes during and after anesthesia^[115,116]. Although efforts have been made to develop standardized guidelines or protocols for the anesthetic care of the obese patient^[117], there is no known ideal anesthesia technique or drug combination. However, the introduction of enhanced recovery after surgery (ERAS) protocols after obesity-related and bariatric procedures has gained great acceptance^[118,119].

Despite the growing body of evidence supporting significant immunomodulatory effects for several

anesthetic agents, there is a paucity of data on anesthetic-mediated immunomodulation in obesity. In this line, two small randomized controlled trials enrolling obese surgical patients evaluated the effects of different anesthetic approaches (Table 1). Abramo *et al*^[120] investigated the effects of total intravenous anesthesia (TIVA), inhalation anesthesia (sevoflurane), or xenon anesthesia on serum levels of proinflammatory cytokines (IL-6, IL-10, TNF- α) and NO. The authors observed that xenon anesthesia was superior to the other two strategies in inhibiting postoperative serum TNF- α concentrations, but found no differences in other mediators^[120]. The effects of ketamine on inflammatory and immune responses after short-duration procedures were similar to those previously reported in non-obese patients^[121].

Inhaled anesthetics exert multiple protective effects that enhance perioperative organ function preservation in humans^[122] and small animals^[2]. Preclinical data have investigated the effects of anesthetic agents on the low-grade chronic inflammation of obesity^[123-128]. These studies focused on the interaction of obesity and the metabolic syndrome with the expected protective effects of IAs, but did not evaluate immune system interactions.

In one study, sevoflurane preconditioning failed to induce cardioprotection in obese animals, in contrast to the effect observed in lean animals^[123]. This negative effect can be explained by reduced activation of the ROS-mediated AMPK signaling pathway^[123]. In another study, van den Brom *et al*^[124] showed that sevoflurane has a stronger depressant effect on myocardial function than other agents, thus possibly increasing cardiac vulnerability to limited oxygen supply and increasing risk of ischemia during surgery.

Concerning the role of adrenergic receptors, the long-term metabolic stress seen in obesity and diabetes type 2 alters type α and β adrenoceptor (AR) function and their interaction with isoflurane anesthesia. Bussey *et al*^[125] showed that isoflurane anesthesia enhanced α -AR sensitivity, normalized β -AR response, and impaired cardiovascular function by reducing hemodynamic compensation during acute stress in experimental obesity and type 2 diabetes. Finally, Zhang

Table 2 Animal studies of effects of inhalational anesthesia in obese or MetS animals

Ref.	Population	Interventions	Comparison	Outcome in obese animals	Outcome in lean animals
Song <i>et al</i> ^[125]	Animals fed high-fat vs low-fat diet	Myocardial ischemia and reperfusion	Ctrl x Sevoflurane preconditioning	No sevoflurane cardioprotection	Sevoflurane: ↓ infarct size; ↑ endothelial nitric oxide synthase, myocardial nitrite and nitrate
van den Brom <i>et al</i> ^[124]	Animals fed western vs control diet	Sevoflurane 2% vs baseline on echocardiographic myocardial perfusion and function	Myocardial perfusion and systolic function	Sevoflurane: No additional effect on myocardial perfusion but impaired systolic function	Sevoflurane: ↑ microvascular filling velocity, no change in myocardial perfusion
Bussey <i>et al</i> ^[125]	Zucker type 2 diabetic Zucker obese vs lean counterpart animals	Conscious vs 2% isoflurane anesthesia	Hemodynamic effects (mean arterial pressure, heart rate) of α or β adrenoreceptor (AR) stimulation	Isoflurane exacerbated and prolonged α-AR sensitivity and normalized chronotropic β-AR responses	Maintenance of ↑ α-AR sensitivity, ↑ chronotropic β-AR heart rate and mean arterial pressure responses
Zhang <i>et al</i> ^[126]	Animals with hypercholesterolemia vs normocholesterolemic animals	60 min sevoflurane pre-treatment, 12 h before myocardial IR surgery	Expression of myocardial iNOS and eNOS	No cardioprotectant effects of sevoflurane, downregulation of eNOS. Interference with iNOS signaling pathway	Delayed sevoflurane cardioprotection: decreased infarct size and improved ventricular function
Yang <i>et al</i> ^[127]	Animals fed high-fat vs low-fat diet	60 min focal cerebral ischemia followed by 24 h of reperfusion 15 min sevoflurane postconditioning	Cerebral infarct volume, neurological score, motor coordination 24 h after reperfusion	Sevoflurane post-conditioning failed to confer neuroprotection; no neuroprotective effect of mitoKATP channel opener	Sevoflurane ↓ infarct size, improved neurological deficit scores; neuroprotective effect of mitoKATP channel opener
Yu <i>et al</i> ^[128]	Animals fed high-fat vs low-fat diet	Middle cerebral artery occlusion; Isoflurane post-treatment after 20 min <i>in vitro</i> ischemia or transient middle cerebral artery occlusion	Cell injury in hippocampal slices, brain infarct volume, neurological deficit	Attenuated isoflurane-induced neuroprotection; ↓ Akt signaling pathway	Isoflurane post-treatment ↓ injury

Summary of the results of experimental studies comparing inhalational anesthetics according to population, intervention, comparison, and outcomes. AR: Adrenergic receptor; eNOS: Endothelial nitric oxide; IR: Ischemia-reperfusion.

et al^[126] showed that the expected cardioprotective effect of sevoflurane against reperfusion injury through interference on myocardial iNOS signaling was absent in hypercholesterolemic rats.

Obesity has been implicated in altering the protective postconditioning effect of sevoflurane anesthesia against cerebral ischemic injury. Molecular analyses demonstrated reduced expression of Kir6.2, a significant mitoKATP channel component in the brain. This reduced Kir6.2 expression may diminish mitoKATP channel activity, contributing to an inability to postcondition the brain against ischemia reperfusion-injury^[127]. Furthermore, in a study of mice fed a high-fat diet, attenuation of neuroprotection was observed after isoflurane exposure in hippocampal slices exposed to oxygen-glucose deprivation. Obese mice exhibited higher levels of carboxyl-terminal modulator protein (CTMP, an Akt inhibitor) and lower levels of phosphorylated Akt than age-matched animals fed a regular diet, suggesting an influence of high-fat diet in decreasing prosurvival Akt signaling in the brain. This may explain the higher isoflurane concentrations required to neuroprotect from oxygen-glucose deprivation in this study^[128]. Table 2 lists recent preclinical studies that assessed the potential cardioprotective and neuroprotective effects of IAs in

animals with obesity and the metabolic syndrome.

One study showed that, apart from cardioprotective effects, 1 h of propofol (but not dexmedetomidine) infusion increased airway resistance and pulmonary inflammation, in an effect mediated by expression of TNF-α and IL-6 in lung tissue^[129]. These results raised questions about the proposed mechanisms of propofol or its lipid vehicles on obesity-associated meta-inflammation.

CONCLUSION

If the immunomodulatory properties of anesthetic agents are indeed demonstrated to have impacts on perioperative care and short-term or even long-term outcomes, this would provide clinicians and researchers with valuable evidence to rethink the use of these agents and improve their usage, particularly in the obese population. A better understanding of the complex relationships and detailed mechanisms whereby anesthetic agents modulate obesity-associated pulmonary inflammation and immune responses is a growing field of study in which additional basic-science and clinical observation data are necessary. Further studies are required to link important pharmacokinetic aspects of these drugs to relevant aspects of lung immune function in obesity-related inflammatory conditions, as well as to identify

the mechanisms of these interactions so that drugs with potential lung-specific immunosuppressive effects can be identified and their impact evaluated. In the very near future, the perioperative care of the obese patient may also be guided by different anesthetic strategies, with careful regard to immune status.

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