The Protective Effect of Propofol on Airway in Asthmatic Patients

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Abstract
Asthma is a chronic inflammatory disease of airway characterized by intermittent airway obstruction and reversible airway hyperresponsiveness (AHR). It presents a major public health problem with increasing prevalence rates and severity worldwide. Patients with no pretreatment suffered from perioperative asthmatic attack and might result in severe complications (such as hypoxemia, pneumonia, pneumothorax, pulmonary barotrauma, prolonged intubation, atelectasis, mucus plugging and so on). Propofol, a widely used short-acting intravenous anesthetic, is recognized as the ideal sedative in asthmatic patients. Results from many clinical observations and laboratory studies strongly support the notion that propofol exerts significant protective effect of asthmatic airways. The mechanisms of airway protection by propofol are complicated, involving the direct relaxation of airway smooth muscle, the attenuation of parasympathetic nerve acetylcholine release, the anti-inflammation properties, the stimulation of ciliary motility and so on. Despite abundant studies about the protective effect of propofol in asthmatic patients, the mechanisms remain to be further developed.

Keywords: Propofol; Asthma; Airway; Protective effect.

Introduction
Asthma is a chronic inflammatory disease of airway characterized by intermittent airway obstruction and reversible airway hyperresponsiveness (AHR). It presents a major public health problem with increasing prevalence rates and severity worldwide [1]. According to the data from World Health Organization (WHO) and Global Initiative for Asthma (GINA), 235-300 million people currently suffer from asthma as of 2011 and approximately 250,000 people die per year from asthma [2,3]. The global prevalence of asthma have increased significantly during the past few decades [4,5]. According to national center for health statistics (NCHS), asthma prevalence increased from 7.3% in 2001 to 8.4% in 2010 in the United States [6].

Surgeries may be inevitable in some asthmatic patients. About 10.2% of asthmatic patients with no pretreatment suffered from perioperative asthmatic attack and might result in severe complications (such as hypoxemia, pneumonia, pneumothorax, pulmonary barotrauma, prolonged intubation, atelectasis, mucus plugging and so on) [7]. The incidence of these peri-operative complications in asthmatic populations reaches up to 30%, which is much higher than that in healthy patients [8,9]. Because of the airway hyperreactivity, bronchospasm may easily be induced by direct airway stimuli (such as laryngoscopy, tracheal intubation, airway suctioning, tracheal extubation and so on), drugs, inadequate depth of anesthesia, surgical stimuli and perioperative complications such as aspiration, infection, or trauma. Therefore, apart from prophylactic treatment of asthma before surgeries, it is vital for anesthesiologists to choose...
the most appropriate anesthetics for asthmatic patients.

Propofol, a widely used short-acting intravenous anaesthetic, is recognized as the ideal sedative in asthmatic patients [10,11]. Results from many clinical observations and laboratory studies strongly support the notion that propofol exerts significant protective effect of asthmatic airways. The mechanisms of airway protection by propofol are complicated, involving the direct relaxation of airway smooth muscle, the attenuation of parasympathetic nerve acetylcholine release, the anti-inflammation properties, the stimulation of ciliary motility and so on. Despite abundant studies about the protective effect of propofol in asthmatic patients, the mechanisms remain to be further developed.

Airway Protective Effect of Propofol

It is widely observed in vitro and in vivo studies that propofol can attenuate the response to a variety of bronchoconstrictor agents in both animals and humans, with hyperreactive or normal reactive airways.

the effect of propofol on normal airways

A growing body of laboratory and clinical studies support the concept that propofol has bronchodilation properties not only in asthmatic airways but also in normal airways.

Results from many studies have shown that propofol decreases airway resistance in patients or animals with normal reactive airways. In normal rats with no previous airway constriction, airway resistance was found to decrease after the rats were anaesthetized with propofol [12]. Likewise, propofol appeared to be superior to thiopental and thiobarbiturate in inhibiting the prevalence of tracheal intubation-induced bronchoconstriction as propofol has been shown to decrease the prevalence of wheezing after the induction of anesthesia and intubation of the trachea in normal patients [11,13]. Compared with thiopental and etomidate, propofol was associated with decreased airway resistance in a randomized trial involving nonasthmatic smokers undergoing general anesthesia [14].

Moreover, it is observed that propofol is shown to have a direct airway smooth muscle (ASM) at concentration of 10^-4M and a greater direct relaxant effect on distal ASM than on proximal ASM[15]. The decrease in airway resistance with propofol anaesthesia was supported by central airway dilation observed at lung histology in normal rats[12].

the effect of propofol on asthmatic airways

A number of studies and reports suggest that propofol may have properties beneficial to patients with asthma. During anesthesia induction, it is observed that the incidences of wheezing and the airway resistance at 2 and 5 min post-intubation were significantly lower in asthmatic patients anesthetized with propofol than with thiopental[11]. When used for sedation, propofol is reported to inhibit postoperative bronchospasm in two patients with hyperreactive airway disease[16]. Moreover, rapid improvement of symptoms was observed in a patient moribund with asthma, shortly after induction of anesthesia with propofol[17]. In vivo studies, intraperitoneal injection of propofol is shown to decrease the airway resistance induced by methacholine in asthmatic mice[18]. In vitro studies, propofol was able to induce concentration-dependent relaxations in precontracted, isolated trachea smooth muscle of asthmatic airways[19,20].

Mechanisms of Airway Protective Effect of Propofol

The Direct Relaxant Effects of Propofol on Airway Smooth Muscle

It is well known that the concentration of intracellular free Ca2+ plays a central role in the regulation of ASM tone, therefore the inhibition of Ca2+ mobilization, decrease of Ca2+ sensitivity, or both may contribute to the ASM relaxant effects of propofol.

The Effects of Propofol on Intracellular Concentration of [Ca2+]

The direct relaxing effect on smooth muscle of propofol has been ascribed to a reduction in the concentration of intracellular concentration of [Ca2+]i[12,14]. The regulation of intracellular Ca2+ ([Ca2+]i) is integrated by two mechanisms which include Ca2+ release from the internal store (sarcoplasmic reticulum, SR) and plasma membrane Ca2+ influx. The mechanism underlying the relaxant effects of propofol might be caused inhibition of Ca2+ release from the internal store and plasma membrane Ca2+ influx[21,22].

de the effects of propofol on Ca2+ release from internal store: Ca2+ release from intracellular...
stores is regulated by two mechanisms: inositol phosphate (IP3)-induced Ca2+ release and Ca2+ induced Ca2+ release[23,24]. It is demonstrated that propofol could attenuate the IP3 production induced by carbachol[21]. IP3 is a second messenger in the M3 receptor-coupled signaling pathway. This finding indicates that propofol may interfere with the components of receptor-G-protein-phospholipase C pathway[21]. However, the precise site of action is not known.

**the effects of propofol on plasma membrane Ca2+ influx:** Ca2+ influx can occur through both voltage-gated[25] and receptor-gated channels[26]. The inhibition of Ca2+ influx may be caused by blockade of L-type voltage-dependent Ca2+ channels[21,22,27]. As it is demonstrated in isolated ASM, [Ca2+]i increase induced by KCl could be inhibited by propofol and this inhibition was blocked by verapamil (the voltage-operated calcium channel blocker)[28]. However, it is demonstrated in some previous studies that the inhibition effect of [Ca2+]i was achieved at concentration higher than those encountered clinically[27].

**The Effects of Propofol on Sensitivity of [Ca2+]i**
Airway smooth muscle contraction is not only attributed to the increase in intracellular Ca2+ ([Ca2+]i) on account of increased tension induced by agonist at the same [Ca2+]i (increase in Ca2+ sensitivity). Evidence shows that propofol dilates contracted ASM through reduction in intracellular Ca2+ by inhibiting influx of Ca2+ and release of intracellular stores, but not by decreased Ca2+ sensitivity[29]. However, conflicting evidence exists, as the study from Grim et al shows propofol may have an impact on Ca2+ sensitivity via RhoA/Rho-kinase pathway[30].

**The Effects of Propofol on Respiratory Nerve System**
It has been well known that the parasympathetic nervous system, adrenergic nerve system and nonadrenergic noncholinergic (NANC) nerve system together form the predominant neural pathway and play an important role in the regulation of airway diameter and resistance to airflow in mammalian airway.

**The Effects of Propofol on Parasympathetic Nerve System**
Propofol was previously reported to be able to decrease basal airway tone similarly to atropine and attenuate histamine-induced bronchoconstriction and it is maybe a reduction in vagal tone that produce the relaxant effect[31]. Brown et al.[32] found that propofol caused a dose-dependent (8.4×10-5 M, 2.8×10-4 M, 8.4×10-4 M) attenuation in the vagal nerve stimulation induced bronchoconstriction. Furthermore, as the spasmylytic effects of propofol did not differ between normal dogs and vagotomized dogs, the relaxant effect of propofol on methacholine-induced bronchoconstriction may be a result of inhibition of the peripheral vagal motor pathway instead of central vagal pathway or direct inhibition of Ca2+ mobilization[33]. The concentrations (100μM) required for these smooth muscle effects in the above mentioned studies are above those typically achieved clinically. Therefore, whether the clinically relevant concentration of propofol relax ASM by inhibiting the vagal motor pathway or not still needs to be further explored.

The Inhibitory Effect of Propofol on Nonadrenergic Noncholinergic Nerve System
Studies in humans and animal airway tissue models demonstrated that propofol could attenuate acetylcholine, histamine, and endothelin-1 induced contractile responses, merely at concentrations above those achieved clinically (1×10-4 M ~3×10-4 M)[21,22]. However, Gleason et al[34] indicated that although propofol at clinically relevant concentration could not attenuate acetylcholine induced ASM contraction, it is able to inhibit tachykinins A (neurotransmitter released by nonadrenergic noncholinergic nerve) induced ASM contraction. This finding suggests that propofol may relax ASM by affecting nonadrenergic noncholinergic (NANC) nerve system.

Studies suggesting a vagal nerve-mediated mechanism for propofol have made two important and perhaps incorrect assumptions of irritant induced bronchoconstriction: (1) cholinergic nerves are the primary airway efferent nerve and (2) acetylcholine is the primary agonist. Nevertheless, stimulated NANC nerves induce bronchoconstriction in animals and humans by liberated neurotransmitters (e.g., tachykinins). Gleason et al [34] applied ten-second trains of square wave direct current electrical field stimulation (30-50 Hz, 24 V, 0.5ms pulse width) to tracheal rings to induce contraction. These electrical
stimuli induced a contractile response with two distinct components: a rapid cholinergic contraction followed by a more slowly developing contraction classic for excitatory (procontractile) NANC contractions. It is found that clinically relevant concentrations of propofol relaxed the NANC component of electrical field stimulation-induced contraction mediated by tachykinins, while have no effect on cholinergic component of electrical field stimulation-induced contraction [34]. Therefore, it is concluded that the mechanism of the protective effect of propofol on irritant-induced bronchoconstriction may be either by decreasing NANC nerve transmission or by attenuating the contractile effect of liberated tachykinins at the neurokinin receptor on the airway smooth muscle itself.

The Immunoregulatory Effect of Propofol on Airway Inflammation

Airway inflammation has emerged as an important contributor to mechanisms of asthma. The immunologic-inflammatory pathways involved in the pathogenesis of asthma are complex and include lymphocytes (both Th1 and Th2), immunoglobulin E, eosinophils, neutrophils, mast cells, leucotrienes, and cytokines [10]. T-helper cell type (Th) lymphocytes play an important role in the initiation, progression and persistence of asthma. The mechanism of action of the “Hygiene Hypothesis” stated that insufficient stimulation of the Th1 arm, stimulating the cell defence of the immune system, leads to an overactive Th2 arm, stimulating the antibody-mediated immunity of the immune systems and playing an important role in induction and aggravation of airway inflammation [35].

The immunoregulatory effect of propofol has been shown in numerous studies that propofol not only can preferably promote Th cells to differentiate into Th1 cells [36,37] but also inhibit effects on cytokines secreted by Th2 cells, such as interleukin 6 (IL-6) and IL-10 in some infectious animal models or human [38,39]. Furthermore, it is currently observed that propofol administration significantly inhibited the elevation of cytokines secreted by Th2 cells (including IL-4, IL-5), while showed no effect on IFN-γ (mainly secreted by in asthma mice, which led to the down regulation of Th1/Th2 ratio 18. However, studies about the effect of propofol on airway inflammation of asthma animals or human are rare recently. Further investigations are yet needed to be conducted.

Other Potential Mechanisms of Protective Effect of Propofol

The Effect of Propofol on Gamma-Aminobutyric Acid (GABA)

It is found that low concentrations of propofol (20 μM) facilitated airway smooth muscle relaxation is likely due to the signaling pathways regulating relaxation rather than those regulating contraction [40]. It is known that propofol is an anesthetic with positive allosteric effects at the GABA channels. It has been a long-standing belief that any potential GABAergic contribution to airway tone is largely mediated by GABAA channels in the brainstem [41] or by GABAB channels on preganglionic cholinergic nerves in the lung [42]. Therefore, propofol may show relaxant effect by acting on GABAA channels in the brainstem or GABAB channels on preganglionic cholinergic nerves in the lung. However, the airway smooth muscle relaxation of propofol may be mediated by enhancing the effect of GABA in the lung. Endogenous GABA was also found to be existing in the airway and plays an important role in modulating airway smooth muscle tone by facilitating smooth muscle relaxation via activation of airway smooth muscle GABAA and GABAB channels [40,41,43]. Gallos et al. [40] demonstrated a dose-dependent improvement in relaxation of a substance P contraction by propofol, which was partially reversed by low-dose GABAA channel antagonism (gabazine, 5 μM). Therefore, the airway smooth muscle relaxation of propofol may be mediated by acting on this novel relaxation pathway.

Propofol Stimulates Airway Ciliary Motility

Clearance of foreign particles, such as dust and bacteria and debris, from the respiratory tract by airway cilia is an important host defense mechanism, which is critical for asthmatic patients [44]. Because the ciliary function is impaired in asthmatic patients, they are predisposed to respiratory infection or atelectasis. Therefore, the use of an anesthetic that does not affect or that promotes ciliary motility may benefit surgical patients with respiratory risk.

It is showed that ciliary beat frequency (CBF) could be stimulated by propofol in a dose-dependent manner (1-100 μM)45. It is suggested that propofol stimulates CBF via the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway in cultured rat tracheal ciliated epithelial cells. As NO and the NO-
cGMP signaling pathway play a pivotal role in regulating ciliary motility in airway epithelium and propofol is proved to be able to stimulate the release of NO and cGMP in cultured tracheal epithelial cells. Therefore, it is indicated that the promotion of ciliary motility is associated with the effect of propofol on the NO-cGMP pathway [45].

**The Effects of Propofol on 5-HT**

It is demonstrated that propofol could abolish 5-HT induced contraction in a dose-dependent manner. It is well known that 5-HT causes contraction of airway smooth muscle through two mechanisms. One is mediated by a direct action of this agonist to the 5-HT receptors of tracheal smooth muscle cell membrane, and the other is by activation of 5-HT receptors on parasympathetic nerve endings. It is suggested that propofol at a higher concentration (3×10−4 M) would abolish both kinds of action of 5-HT [46].

**The Effect of Preservatives in Propofol on Airway Smooth Muscle**

Currently, EDTA and metabisulfite are the most used formulations as preservatives in propofol. According to Nishiyama et al., the effect of propofol on airways differs with the formulation of the drug used [47]. The preservative used for propofol formulation may alter the effects of propofol on the total respiratory system resistance in smokers. Previous work showed that the infusion of propofol without metabisulfite could attenuate bronchoconstriction in an animal model [48] and in humans [13,22]. However, propofol with metabisulfite had no effect on vagal nerve stimulation-induced bronchoconstriction. Therefore, it is estimated that the preservative (metabisulfite) used for propofol can have a dramatic effect on its ability to attenuate bronchoconstriction. As studied in previous research, metabisulfite has been shown to cause airway narrowing in asthmatic animals and humans [49,50]. Because of the similarity of the airway response to the VNS- and methacholine-induced bronchoconstriction during metabisulfite infusion, it is suggested that metabisulfite affects are through direct airway smooth muscle mechanisms to cause airway hyperresponsiveness [51].

On the contrary, the formulations of propofol containing EDTA (ECP) or propofol without preservatives (widely available outside of US) have been reported previously to offer more protection against tracheal intubation induced bronchoconstriction than other induction agents (i.e., thiopental and etomidate) [14,51]. The total respiratory system resistance measured repeatedly for 10 min after tracheal intubation in patients with smoking history or in sheep after metacholine challenge is significantly decreased after induction with EDTA-containing propofol than after induction with sulfite [52].

**Summary**

Asthmatic patients who undergo surgeries may suffer from perioperative asthmatic attack and might result in severe complications. Propofol has shown airway protection by attenuating concentration of intracellular Ca2+, decreasing vagal motor tone, stimulating airway ciliary motility, inhibiting airway inflammation, the regulating effect of GABA receptors, 5-HT and NANC nerve system and so on. Propofol might show great strength as an anesthetic or sedative in clinical practice for asthmatic patients.

**References:**


