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Review

Sedating Mechanically Ventilated COVID-19 Patients with Volatile Anesthetics: Insights on the Last-Minute Potential Weapons

Aiman Suleiman [1,*], Abdallah Barjas Qaswal [2,*], Mazen Alnouti [1], Moh'd Yousef [1], Bayan Suleiman [1], Mohammad El Jarbeh [1], Ghadeer Alshawabkeh [3], Isam Bsisu [1], Abeer Santarisi [4] and Muaweih Ababneh [5]

1 Department of Anesthesia and Intensive Care, School of Medicine, The University of Jordan, Amman 11942, Jordan; Mazen.alnouti@yahoo.com (M.A.); Yousefmohammad1993a@gmail.com (M.Y.); Bayan.suleiman93@gmail.com (B.S.); Mhmd.sum@hotmail.com (M.E.J.); Isam_Bsisu@hotmail.com (I.B.)
2 Department of Internship Program, School of Medicine, The University of Jordan, Amman 11942, Jordan
3 Department of Anesthesia and Intensive Care, King Hussein Cancer Center, Amman 11942, Jordan; Shawabkehgk@gmail.com
4 Department of Emergency Medicine, School of Medicine, The University of Jordan, Amman 11942, Jordan; Abeer_santarisi@yahoo.com
5 Department of Anesthesia and Intensive Care, Alabdali Clemenceau Hospital, Amman 11190, Jordan; Muaweih.ababneh@abdalimedical.com
* Correspondence: Aiman.majed@yahoo.com (A.S.); qaswalabdullah@gmail.com (A.B.Q.)

Abstract: Coronavirus Disease 2019 (COVID-19) has spread globally with the number of cases exceeding seventy million. Although trials on potential treatments of COVID-19 Acute Respiratory Distress Syndrome (ARDS) are promising, the introduction of an effective therapeutic intervention seems elusive. In this review, we explored the potential therapeutic role of volatile anesthetics during mechanical ventilation in the late stages of the disease. COVID-19 is thought to hit the human body via five major mechanisms: direct viral damage, immune overactivation, capillary thrombosis, loss of alveolar capillary membrane integrity, and decreased tissue oxygenation. The overproduction of pro-inflammatory cytokines will eventually lead to the accumulation of inflammatory cells in the lungs, which will lead to ARDS requiring mechanical ventilation. Respiratory failure resulting from ARDS is thought to be the most common cause of death in COVID-19. The literature suggests that these effects could be directly countered by using volatile anesthetics for sedation. These agents possess multiple properties that affect viral replication, immunity, and coagulation. They also have proven benefits at the molecular, cellular, and tissue levels. Based on the comprehensive understanding of the literature, short-term sedation with volatile anesthetics may be beneficial in severe stages of COVID-19 ARDS and trials to study their effects should be encouraged.

Keywords: sedation; COVID-19; ARDS; respiratory failure; volatile anesthetics; mechanical ventilation

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1. Introduction

The first case of COVID-19 (Coronavirus Disease 2019) was reported in the city of Wuhan, China. Soon after, cases were reported in more than 170 countries across the world. As of December 2020, the number of cases worldwide has exceeded 70 million, with more than 1.7 million deaths. Although many ongoing trials of potential treatments are promising, the introduction of an effective therapeutic intervention to the medical market seems elusive. Hence, shedding light on the possible roles of some of the regularly used drugs could lead us to achieve a fair degree of success in facing the pandemic.

As the name of the virus 'SARS-CoV-2' (Severe Acute Respiratory Syndrome Coronavirus 2) implies, COVID-19 can progress to a cytokine storm that strikes the lungs, leading to ARDS (Acute Respiratory Distress Syndrome) [1,2]. In patients presenting with COVID-19 pneumonia, 42% can develop ARDS [3]. The typical ARDS mortality rate in

the ICU (Intensive Care Unit) reaches 35% [4], while mortality from COVID-19 ARDS in patients admitted to ICU is nearly 60% and reaches 90% if the patient requires mechanical ventilation [5,6]. Hence, respiratory failure resulting from ARDS is the most common cause of death in COVID-19 [7]. Through a comprehensive understanding of the pathophysiology of the disease, insights from the literature could lead us to possible therapeutic solutions. We aim to discover the potential role of inhalational anesthetics in reversing or slowing down the progress of COVID-19 ARDS when given as short-term sedative agents for mechanically ventilated patients.

2. COVID-19 ARDS Pathophysiology

The pathophysiology of SARS-CoV-2 infection resembles that of SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) infection, with inflammatory responses being responsible for damaging the airways [8]. Some patients may be at risk of secondary bacterial and fungal infections [8,9]. When the virus is introduced to the body, the RBD (Receptor-Binding Domain) on the S1 subunit of S protein of the virus will bind to the ACE2 (Angiotensin-Converting Enzyme 2) and TMPRSS2 (Transmembrane Serine Protease 2) proteins on the epithelial cell surface, triggering endocytosis [10–17]. The virus then replicates to release many copies of itself. The cell then undergoes pyroptosis (which is a form of programmed cell death that potently triggers immune responses [18,19]) and releases damage-associated molecular patterns like ATP (Adenosine Triphosphate), nucleic acids and ASC oligomers [11]. This inciting event is recognized by the neighboring resident epithelial cells, endothelial cells, and macrophages, causing the release of pro-inflammatory cytokines such as IL-6 (Interleukin-6), IP-10 (Interferon gamma-induced protein 10), G-CSF (Granulocyte colony-stimulating factor) and macrophage inflammatory proteins [7,20,21]. Viral infection can also activate the NLRP3 inflammasome (Nod-like receptor family, pyrin domain-containing 3) through cellular hyperpolarization, which occurs due to disturbances in the K^+ and Ca^{2+} flux mediated by 3a and E viral proteins [22–31], the release of reactive oxygen species, or direct signals from mitochondrial DNA (Deoxyribonucleic acid) after cell damage [32,33]. When activated, the NLRP3 inflammasome binds to mitochondrial proteins to catalyze a proteolytic process of pro-IL-1β and pro-IL-18 into their active forms [34,35]. These cytokines will attract neutrophils, natural killer cells, monocytes, macrophages and T cells to the site of injury. These cells will eventually accumulate in the lungs, leading to the overproduction of pro-inflammatory cytokines and a cytokine storms [20,36–38].

COVID-19 ARDS is a spectrum of COVID-19 cytokine storms, which reflects the vast release of cytokines from T cells and macrophages in response to the viral infection [7,39]. It is confirmed when a patient with viral pneumonia meets Berlin ARDS diagnostic criteria [4,5]. As severity increases and mechanical ventilation becomes mandatory, high levels of CRP (C-reactive protein), CK (Creatinine Kinase), neutrophil count, interleukins (IL-2, IL-6, IL-7, IL-1β), TNF-α (Tumor Necrosis Factor α), interferon γ and D-dimers are usually detected in serum [6,21,40]. This implies that severe stages of the disease are strongly related to immune overactivation. In addition, lymphocytic count decreases as the disease progresses [6,41,42]. Notably, levels of immune-suppressive IL-10 (Interleukin 10) markedly increase in parallel with disease severity [43]. Cellular damage along with the released cytokines will activate the adaptive immunity, represented by T and B lymphocytes [21]. Mass cytometry on lung tissues demonstrated diffuse infiltration of CD4+ T lymphocytes and macrophages, with patchy infiltrations of natural killer cells, neutrophils, and mature T cells [44]. Histological findings include diffuse alveolar damage along with severe pulmonary microthrombosis [38,45].

The main pathology in COVID-19 ARDS is damage to the alveolar epithelial cells and endothelial cells through inflammatory cell infiltration that accumulates proteases and reactive oxygen species [37,38,46]. In severe status, high viral load is directly related to poor outcome [47]. Thrombotic Disseminated Intravascular Coagulation (DIC) was noted in most deaths related to COVID-19 ARDS [48]. Autopsy tissues showed very high levels of

TNF-α, IL-1β, and IL-6 [49]. Interestingly, highly inflammatory monocyte-derived FCN1+ macrophages with CD14+ and CD16+ monocytes were found in the bronchoalveolar lavage fluid of patients with severe COVID-19 [20,50].

Despite the fact that COVID-19 ARDS is mainly a manifestation of overactive immunity, the immune response plays an important role in fighting the virus. CD4+ T cells are very important for priming the response of CD8+ T cells and B cells and recruiting more immune cells through cytokine production [51]. The CD8+ T cells are directly involved in attacking the virus-infected cells [52]. The depletion of CD4+ and CD8+ T cells can slow viral clearance and hasten lung inflammation [53,54]. The B cells attack the N (Nucleocapsid) protein and the S protein of the virus [55,56], and polyclonal antibodies from convalescent plasma have proven efficacy in decreasing viral load and mortality [57].

In this sense, we conclude that severe stages of COVID-19 ARDS are mostly related to immune dysregulation, direct viral damage, and possibly pulmonary thrombosis. Hence, a comprehensive approach at this late stage of the disease should target these three pathological mechanisms [20].

3. The Potential Therapeutic Role of Volatile Anesthetics

To balance the facts, when COVID-19 worsens, the host response is more damaging than the virus itself [20]. This view is supported by the ongoing trials on potential treatments of the disease, where the main mechanism of action of most drugs tested is immunosuppression [58–66]. Hence, agents that show major immunosuppressive effects with some balancing activating effects should be ideal for countering the disease.

Macrophages are the first responders to infection as they reside in tissues [36]. Sevoflurane and Desflurane reduce macrophage levels in bronchial alveolar fluid, with overall cellular infiltration also reduced [67]. Isoflurane was shown to decrease macrophage release of TNF-α, IL-6, IL-1β, Monocyte Chemotactic Protein-1 (MCP-1) and Macrophage Inflammatory Protein-2 (MIP-2) [68,69]. Regarding cytokines, there are two main classes that regulate the immune response: pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α and Interferon-γ, and anti-inflammatory cytokines like IL-1α, IL-10, TNF-β [36]. Multiple studies were conducted to evaluate the precise effect of each volatile agent on the different classes of cytokines. Though some studies showed some volatile agents might potentiate inflammatory cytokines, the prominent general model extracted from numerous other studies points to a potent inhibitory effect of volatile agents on pro-inflammatory cytokines, with a stimulatory effect on anti-inflammatory cytokines [36,68,70–90]. In brief, volatile agents seem to have a rather balancing effect on immunity where many studies proved their ability to attenuate pro-inflammatory and potentiate anti-inflammatory cytokines, but there are some studies that suggest these agents might not impact or paradoxically potentiate the immune response. While keeping in mind that immunosuppression is mostly in favor of other effects, the balancing effects reported in the literature can be viewed as a beneficial aspect of these agents [68].

Neutrophils are among the first and most lethal immune cells recruited to the site of inflammation [91]. Inhalational anesthetics decrease neutrophilic adhesion, phagocytic function, and reactive oxygen species production [79,92,93]. Sevoflurane was also shown to decrease neutrophilic count [92]. The inhibition of neutrophilic adhesion spares the deleterious effects of Polymorphonuclear (PMN) cell accumulation and protects the remaining healthy tissues [36]. This can be supported by the reported beneficial effects of general anesthesia to post-ischemic cardiac function [94,95]. Trials on mice exposed to volatile agents showed decreased PMN cells level in BAL (Bronchoalveolar Lavage), neutrophil-attracting chemokines, and severity of symptoms when mice were injected with a sublethal dose of the Influenza A virus [96,97]. Some studies suggested that volatile agents do not affect proliferation of PMN cells, which might be a balancing effect [98]. Other cells affected include natural killer cells, which have a vital role against viral infections. Isoflurane was shown to decrease natural killer cells' response to interferon, while Sevoflurane reduces their cytokine release [71,99,100]. A decrease in the number of natural killer cells was also

noted following the use of volatile agents [100,101]. Regarding microglia, they are resident tissue cells that potentiate inflammation through cytokine release, but data regarding the effects of volatile agents on these cells are conflicting [83,102,103].

Platelets play an important role in cellular adhesion and coagulation. Sevoflurane enhances P-selectin expression on platelets to potentiate the immune cells' binding ability [104]. Though it did not affect intra-operative blood loss, nor coagulation studies, Sevoflurane can significantly inhibit platelet aggregation [105,106], a property that can be very beneficial in COVID-19 induced microthrombosis [107].

With regard to adaptive immunity, volatile agents decrease proliferation and increase apoptosis of T lymphocytes [93,108–110]. Desflurane preserves Th1/Th2 (T helper cells) and IL-2/IL-4 values [111], while Isoflurane and Sevoflurane decrease Th1/Th2 values [101,112]. B lymphocytes modify their surface receptors or immunoglobulins to be able to recognize pathogens [91]. Their products constitute the most selective and specific part of the immune system. Sevoflurane, Isoflurane and Desflurane can cause B lymphocyte damage through the enhancement of Ca^{2+} release from its endoplasmic reticulum [113,114]. Reports regarding the effects of inhalational agents on the complement system are lacking [36], though general anesthesia is generally associated with a decrease in complement levels [93]. In brief, volatile agents were mostly immunosuppressive with some selective activation, which is exactly what we need in the late stage of COVID-19 ARDS.

As an overview, volatile agents were able to affect all forms of innate and adaptive immunity. They can also inhibit platelet aggregation. Interestingly, volatile agents can inhibit and potentiate macrophages at the same time, depending on the anatomical site of inflammation [36]. Although the literature points to uncountable benefits, long-term exposure to volatile agents can lead to immune dysfunction, increase the viral and the bacterial load, and worsen the outcome in settings of sepsis [115–117]. Hence, in patients with a septic profile, this aspect should be kept in mind, as the patient might already have impaired immunity. Another drawback of volatile agents is their ability to enhance hyperpolarization of the cellular membrane, which is a key step in the pathway of cytokine production through NLRP3 inflammasome activation [118–121].

Among the important effects of volatile agents in the speculation about their ability to treat COVID-19 ARDS is their antiviral effect. The replication of many animal viruses was moderately inhibited by halothane exposure at 2.2% concentration [122]. The studies that evaluated measles virus replication in cellular culture showed a reduction in the appearance of viral replicants at relevant clinical concentrations of the commonly used volatile agents [123,124]. In addition, ether solvents possess the property of disinfection, and diethyl ether was one of the commonly used agents in general anesthesia induction. Since the MAC value of diethyl ether is 2%, its blood concentration might reach a level that is enough to affect the virus directly [125].

4. Favorable Specifics of Volatile Anesthetics in ARDS Sedation

The ideal sedative agent should have fast onset and offset, with a short context-sensitive half-life. Currently, none of the IV (Intravascular) anesthetic agents used is ideal [126]. Volatile anesthetics have been used as sedatives in intensive care settings in Europe and Canada [127,128]. The commonly used agents are Isoflurane, Sevoflurane and Desflurane [129]. Inhalational agents' context-sensitive half-lives are comparable and do not increase in relation to period of administration [130]. All forms of anesthesia are able to modulate the immune system and affect innate and adaptive immunity, but volatile agents possess favorable properties [98,108,131,132]. Multiple studies have shown that sedation with volatile anesthetics over midazolam and propofol was associated with a decrease in time of mechanical ventilation [133–137]. Early extubation is very beneficial in terms of reduction in ventilator-associated complications like volutrauma, atelectasis, and pneumonia [129]. Other studies showed a reduction in post-extubation agitation and delusion, and preservation of factual ICU memory when patients were sedated with volatile agents [138–140]. Studies concerning the effects of volatile agents on ICU delirium

are lacking [129]. In a study on patients with lung diseases on ventilators, the group sedated with Isoflurane had significantly lower mortality than those sedated with propofol or midazolam [140]. Volatile agents can also improve consequences of ARDS. In a prospective study, researchers compared PaO_2/FiO_2 in ARDS patients who received midazolam or Sevoflurane for a 48-h sedation, they found that the Sevoflurane group showed higher PaO_2/FiO_2 [141]. Other studies showed that general anesthesia with inhalational agents over IV anesthetics was associated with lower pulmonary complications and reduced mortality after cardiac and non-cardiac surgeries [142,143]. In surgeries requiring one-lung ventilation, Sevoflurane was associated with fewer pulmonary complications, better oxygenation, and lower pro-inflammatory mediator levels than propofol [117,144]. In sepsis models, Isoflurane showed the ability to decrease neutrophil recruitment over propofol [145,146]. Additionally, Isoflurane attenuated lung injury in post-hemorrhagic shock, but phenobarbital did not [147]. In a ventilator induced lung injury model, Isoflurane and Sevoflurane could attenuate neutrophilic recruitment more than ketamine and Desflurane [148]. However, though never evaluated in diseased lungs, volatile anesthetics worsen V/Q mismatching in healthy individuals [129,149,150].

Volatile anesthetics can also directly affect lung cells in ARDS. Isoflurane could decrease the cytokine-based recruitment of neutrophils following LPS (Lipopolysaccharide) instillation induced injury [97,151]. In other studies, both Isoflurane and Sevoflurane were able to attenuate the pro-inflammatory response of alveolar epithelial cells through their effect on type A γ-aminobutyric acid receptors (GABAa receptors) [152,153]. They also cause bronchodilation through activation of GABAa receptors, hence improving lung and tissue oxygenation [154,155]. Due to unknown reasons, volatile agents can shift the oxygen–hemoglobin dissociation curve to the right, increasing the release of O_2 from hemoglobin to tissues and improving tissue oxygenation [156]. Regarding effects at the tissue level, Sevoflurane mitigates pulmonary oedema through the activation of the amiloride-sensitive Na^+ channel (ENaC) and Na^+/K^+-ATPase on the epithelial cell surface [157], and was also associated with less oxidative burst and lower levels of inflammatory mediators in BAL during mechanical ventilation [158]. In an LPS hit model of lung injury, Isoflurane and Desflurane were able to maintain the integrity of alveolar–capillary membrane [122]. In brief, adding to their immunomodulatory, antiviral and antithrombotic effects, volatile anesthetics were more beneficial than IV agents at the cellular and tissue levels in the settings of ARDS. Their short-term use can also spare some of the complications of the long-term use of IV anesthetics like PRIS (propofol infusion syndrome) [156].

5. Practical Obstacles and Physiological Barriers of Inhalational Sedation

The conduction of inhalational sedation in the ICU settings still has many considerations and practical obstacles. Volatile anesthetics are used in the operation rooms where ventilators are specifically equipped for this purpose, but ICU ventilators use high flow non-rebreathing circuits, which cannot incorporate traditional plenum vaporizers [129]. A couple of solutions to counter this problem were raised, including the use of miniature vaporizers, but issues like large dead space and lack of proper scavenging systems still limit their use at wide ranges [159]. Other limitations are typically circumstantial, for example, sedation using volatile agents should only be conducted by certified anesthesiologists or anesthesiology trained intensivists [160]. The potential complications of volatile anesthetics and the consequences of environmental air pollution with these agents should be properly monitored [161]. The education of ICU staff in the recognition and management of malignant hyperthermia reaction should accompany the implementation of inhalational sedation, and adequate stocks of dantrolene and activated charcoal filters should be readily available.

Though multiple studies suggested the relative safety of volatile anesthetics in patients with multiple comorbidities [133,141,162], these agents are not risk-free. Volatile agents cause dose-dependent respiratory depression and hypotension, along with varying degrees of hypnosis in response to adopted dosing regimens [160]. One study suggested that

long-term use of Sevoflurane may rarely be associated with diabetes insipidus [163]. Other known side effects include malignant hyperthermia, allergy, and hepatitis. Arrhythmogenic agents like halothane must be avoided in the ICU setting, as halothane–epinephrine induced arrhythmias in ICU patients could be fatal [164]. Once sedation commences, regular assessment of pain, delirium and predetermined sedation score is mandatory [160]. For light sedation purposes, dosing regimens as low as 2–5 mL/h Isoflurane or 3–8 mL/h Sevoflurane can be adequate as starting levels. Increments of 0.5–1 mL/h can be used when needed [160]. Routine monitoring as recommended by ASA (American Society of Anesthesiology) guidelines is required, with the addition of the monitoring of end-tidal Minimal Alveolar Concentration (MAC). An end-tidal MAC of 0.2–0.5 typically achieves most sedation goals, with some variations seen in elderly and people with multiple comorbidities and encephalopathy [165]. The provision of volatile agents comes with the price of extra care for maintenance; this includes some daily device changes to preserve humidity and antimicrobial functions, taking extra caution during disconnection of circuits to prevent aerosolization of SARS-CoV-2 with vapor droplets, and the regular checking of scavenging systems to keep occupational levels of volatile agents acceptable.

6. Conclusions

Though mostly mild, COVID-19 might manifest as severe pneumonia progressing to ARDS and eventually death. Severely ill patients may require mechanical ventilation with sedation. Due to practical reasons, volatile agents are not widely used or adequately studied for sedation in ICU [141]. Till now, studies on patients with ARDS from causes other than COVID-19 have proven the beneficial effects of inhalational over IV sedation in terms of tissue oxygenation and mortality [141]. Since the severity of lung injury in COVID-19 is directly related to the levels of cytokines and viral load [166], we suggest that inhalational agents could potentially decrease the severity of the disease. Inhalational agents may mitigate the progression of the disease through many mechanisms: near-balanced immunosuppression, antiviral properties, antithrombotic effects, preservation of membranous and cellular integrity, improvement of tissue oxygenation and bronchodilation. Inhalational sedation is practical, of low cost, and easily controlled. It also meets ASA safety guidelines for COVID-19 patients' sedation [167,168]. Trials on inhalational sedation for COVID-19 ARDS are being conducted [169]. Multiple literature reviews suggested the relative safety and efficacy of using inhalational sedation in late stages of COVID-19 [160,170]. Another review suggested the usage of inhalational sedation as a reliable substitute in the case of an IV anesthetics shortage [171]. The COVID-19 pandemic constitutes an emerging opportunity to study the scientific and practical aspects of inhalational sedation implementation in ICU settings. According to the insights mentioned above, the use of volatile anesthetics for short-term sedation may be beneficial in settings of severe COVID-19 ARD. Reliable recommendations can be constructed after clinical trials confirm benefits. Figure 1 discloses a summary of the beneficial and adverse events associated with the use of volatile anesthetics for sedating mechanically ventilated COVID-19 ARDS patients.

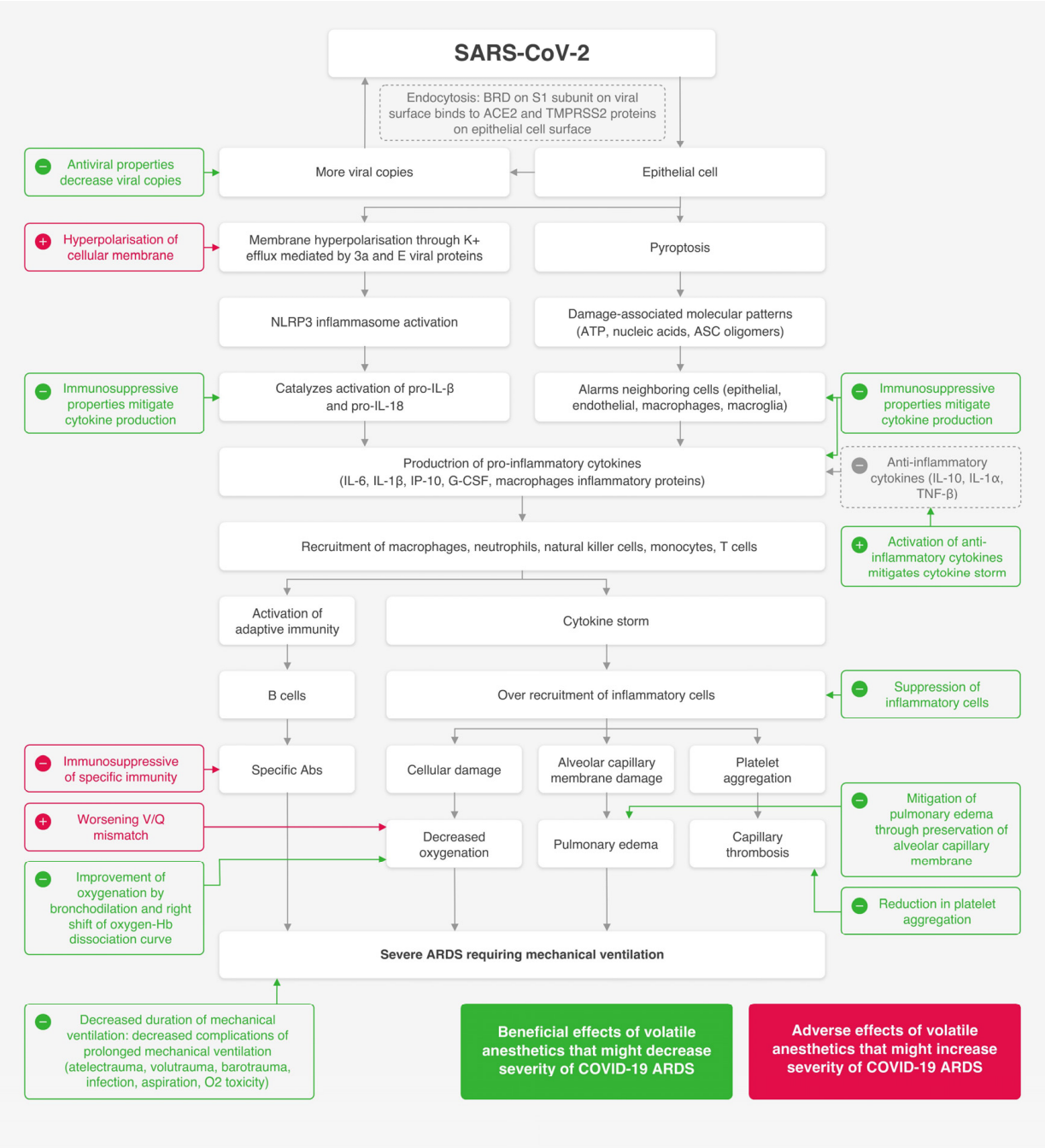

Figure 1. A summary of beneficial and adverse events associated with the use of volatile anesthetics for sedating mechanically ventilated COVID-19 ARDS patients.

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