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**COVID Review****A Critical Appraisal of the Effects of Anesthetics on Immune-system Modulation in Critically Ill Patients With COVID-19**

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**ABSTRACT**

**Purpose:** The aim of the present article was to briefly summarize current knowledge about the immunomodulatory effects of general anesthetics and the possible clinical effects of this immunomodulation in patients with COVID-19.

**Methods:** The PubMed, Scopus, and Google Scholar databases were comprehensively searched for relevant studies.

**Findings:** The novel coronavirus causes a wide spectrum of clinical manifestations, with a large absolute number of patients experiencing severe pneumonia and rapid progression to acute respiratory distress syndrome and multiple organ failure. In these patients, the equilibrium of the inflammatory response is a major determinant of survival. The impact of anesthetics on immune-system modulation may vary and includes both pro-inflammatory and anti-inflammatory effects.

**Implications:** Inhibition of the development of severe inflammation and/or the enhancement of inflammation resolution by anesthetics may limit organ damage and improve outcomes in patients with COVID-19. (*Clin Ther.* 2021;43:e57–e70) © 2021 Elsevier Inc.

**Key words:** acute respiratory distress syndrome, anesthetics, COVID-19, inflammation, multiple organ dysfunction syndrome.

**INTRODUCTION**

Since February 20, 2020, the day of the designation of coronavirus disease by the World Health Organization,<sup>1,2</sup> COVID-19 has spread to include millions worldwide, with confirmed cases increasing

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again despite austere applied measures. This novel coronavirus causes a wide spectrum of clinical manifestations, with a large absolute number of patients experiencing severe pneumonia and rapid progression to acute respiratory distress syndrome (ARDS) and multiple organ failure.

The virus may spread through the respiratory mucosa and infect other cells, inducing a cytokine storm in the body. Infected patients have high amounts of interleukin-1 $\beta$ , interferon  $\gamma$ , interferon  $\gamma$ -induced protein 10, and monocyte chemoattractant protein 1, while a typical patient with pneumonia in whom ARDS develops has a significantly higher neutrophil count, lymphopenia, and more severe cytokine storm than do those without ARDS.<sup>1</sup> Moreover, patients requiring admission to the intensive care unit have higher concentrations of inflammatory mediators and cytokines than do those who are not admitted to the intensive care unit, suggesting that the cytokine storm is associated with disease severity.<sup>2</sup> In addition, severely ill patients have high levels of pro-inflammatory cytokines, including interleukins 2, 6, 7, and 10; granulocyte colony-stimulating factor; interferon  $\gamma$ -induced protein 10; tumor necrosis factor (TNF)- $\alpha$ ; and procalcitonin.<sup>2,3</sup>

Critically ill patients with COVID-19 and acute hypoxemic respiratory insufficiency or failure require early endotracheal intubation and mechanical ventilation. Rapid-sequence induction (RSI), the recommended technique for anesthesia induction, and cautious administration of anesthetic agents may be required. In general, the principles of airway management are like those in more controlled settings, with several drugs being recommended for RSI in patients with COVID-19.<sup>4</sup>

Although general anesthetics may affect the immune system and may increase morbidity and mortality in patients with COVID-19, surprisingly few attempts to cover this issue have been made. The aim of the present article is to briefly summarize some aspects of current knowledge about the immunomodulatory effects of general anesthetics and the possible clinical effects of this immunomodulation in patients with COVID-19.

## MATERIALS AND METHODS

The PubMed, Scopus, and Google Scholar databases were comprehensively searched for English-language, articles published between 1950 and 2020, using the key terms *anesthesia*, *anesthetics*, *inflammation*, *immunomodulation*, *immune modulation*, and

*proinflammatory*. The reference lists of identified articles were searched manually for additional papers eligible for inclusion. Data from articles that were in non-English language were excluded from the review.

## RESULTS

A total of 702 articles were identified from the database searches. After the exclusion of 652 articles based on population, outcomes, research method, results of the studies, or duplicates, data from 50 articles (N = 13,786) were included in the present appraisal.

### Anesthetic Preferences in Patients with COVID-19

The choices of anesthetics may differ between hospitals, cities, or countries, depending on physicians' preferences and availability. To date, only two published studies have reported on the use of induction agents in COVID-19.<sup>5,6</sup> Propofol was used in almost all patients, usually combined with other agents, while midazolam and etomidate were used in only a few patients. Neuromuscular blocking agents were used in all patients, with rocuronium being administered in 99% of patients (Table 1). In both studies, the choice of induction agents was usually dictated by hemodynamic considerations and not by the patient's inflammatory status.

### Immunomodulatory Properties of IV Anesthetic Agents

*Innate immunity*, the first line of defense, refers to protective mechanisms that are present before infection, and is facilitated by the epithelial membranes, phagocytic cells, dendritic cells (DCs), natural killer cells, and several plasma proteins. The most important cellular reaction of innate immunity is inflammation, which is mediated by DCs and natural killer cells. *Adaptive immunity* is facilitated by mechanisms that are induced by the recognition of specific pathogen antigens and is mediated primarily by lymphocytes. However, an inflammatory immune response may also be induced by noninfectious stimuli; for example, anesthesia itself may induce an inflammatory response in some patients. Also, endotracheal intubation does not guarantee a complication-free procedure; local inflammatory response secondary to the presence of the endotracheal tube has been described.<sup>7</sup>

The impact of anesthetics on immune-system modulation may vary and includes both pro- and

anti-inflammatory effects.<sup>8</sup> Although these effects were first demonstrated >100 years ago, research to date has shown that at concentrations used clinically, different anesthetics affect the functions of the inflammatory response in a diverse manner<sup>9</sup> (Table II). Therefore, the development of therapeutic approaches seems prudent for preventing iatrogenic harm that may lead to dysregulation of this inflammatory process and increased morbidity and mortality.<sup>77</sup> The effects of anesthetics on immunomodulation of inflammation are complex, and in patients with COVID-19, the choice and use of these agents must be highly dependent on the immune status, especially in those with obesity, in whom the inflammation-induced synergistic conversion of tissue-resident macrophages to an M1-like phenotype and the expression of cytokines and adipokines by adipocytes will aggravate the inflammatory status.<sup>78–80</sup>

Another important contribution of anesthetics is the potent enhancement of inflammation resolution. It is known that endogenous proresolving bioactive mediators can terminate the inflammatory response by promoting the clearance of cellular debris and countering the release of pro-inflammatory cytokines/chemokines.<sup>81</sup> A loss of inflammation-resolution mechanisms in infectious diseases sustains pathologic inflammation,<sup>79,82</sup> and thus, it may also be involved in the preservation of dysregulated inflammation and associated mortality in COVID-19.<sup>83–85</sup> The resolution of inflammation is also stimulated by a pathway involving the arachidonic acid-derived epoxyeicosatrienoic acids (EETs). These mediators modulate ion transport and gene expression, produce vasorelaxation, promote clearance of cellular debris, and activate anti-inflammatory programs to inhibit several key pro-inflammatory cytokines.<sup>82</sup> Various anesthetic agents can modify these processes. It is known that leukotrienes are metabolites of arachidonic acid derived from the activity of 5-lipoxygenase.<sup>86</sup> Propofol may inhibit 5-lipoxygenase and decrease the production of leukotrienes in DCs and possibly other types of immune and nonimmune cells.<sup>24</sup> Also, dexmedetomidine has been shown to up-regulate netrin-1, an orchestrator of inflammation resolution, resulting in the up-regulation of proresolving (lipoxin) and down-regulation of pro-inflammatory (leukotriene B4) humoral mediators.<sup>60</sup> The shift of arachidonic acid metabolism to favor inflammation resolution enhances the production of

EETs from arachidonic acid by cytochrome P-450 epoxygenases.<sup>87,88</sup> The enhancement of the production of EETs from arachidonic acid by cytochrome P-450 epoxygenases is very important in patients with low-grade or chronic inflammation, in whom the mitigation of disease severity should be a priority. This mitigation can be further enhanced by the propofol-induced suppression of cyclooxygenase enzyme activity.<sup>89</sup> However, ETTs are pulmonary vasoconstrictors and are rapidly metabolized to less-vasoactive dihydroxyeicosatrienoic acids by soluble epoxide hydrolase.<sup>82,88,90–92</sup> Therefore, the administration of propofol may be more effective in the early stages of inflammation, while in advanced respiratory failure with cytokine storm, propofol may be better administered in combination with a soluble epoxide hydrolase inhibitor (eg, urea, carbamate, or amide derivatives) and a pulmonary vasodilator (eg, IV epoprostenol or inhalational iloprost) to decrease lung inflammation and improve lung function.<sup>93</sup>

**Table I. Demographic characteristics and data on airway management from published studies in patients with COVID-19.**

Patient Characteristics	No. (%) of Patients (N = 222)
Sex <sup>5,6</sup>	
Male	147 (66)
Female	75 (34)
Medication <sup>5,6</sup>	
Rocuronium	220 (99)
Propofol	214 (96)
Sufentanil	99 (45)
Fentanyl	60 (27)
Midazolam	27 (12)
Etomidate	6 (3)
Succinylcholine	2 (1)
Oxygen therapy technique <sup>5,6</sup>	
Noninvasive ventilation	160 (72)
High-flow nasal cannula	31 (14)
Mask with reservoir bag	21 (9)
Regular nasal cannula	8 (4)
Survival	
24 h <sup>5,6</sup>	28 (13)
7 d <sup>6</sup>	10 (5)
30 d <sup>6</sup>	8 (4)

Table II. Immunomodulatory properties of common IV anesthetic agents.

Agent	Immunomodulation
Midazolam	<p>Binds to peripheral receptors on macrophages and modulates their metabolic oxidative responsiveness<sup>10</sup></p> <p>Inhibits human neutrophil function and the activation of mast cells induced by TNF-<math>\alpha</math><sup>11</sup></p> <p>Suppresses expression of IL-6 mRNA in human blood mononuclear cells<sup>11</sup></p> <p>Suppresses monocyte chemotaxis<sup>12</sup></p> <p>Suppresses the respiratory burst of reactive oxygen species, inhibits NF-<math>\kappa</math>B activation via suppression of I<math>\kappa</math>B-<math>\alpha</math> degradation, and inhibits p38 activation in lipopolysaccharide-stimulated macrophages<sup>13</sup></p> <p>Suppresses the lipopolysaccharide-stimulated immune responses of human macrophages via translocator protein signaling<sup>14</sup></p> <p>Reduces extracellular IL-8 accumulation by diminishing its secretion from polymorphonuclear leukocytes, despite constantly high intracellular levels and mRNA expression of IL-8<sup>15</sup></p>
Propofol	<p>Suppress oxidative burst formation in TNF-<math>\alpha</math>-primed neutrophils<sup>16</sup></p> <p>Attenuates TNF-<math>\alpha</math>-modulated occludin expression by inhibiting Hif-1<math>\alpha</math>/VEGF/VEGFR-2/ERK signaling pathway in hCMEC/D3 cells<sup>17</sup></p> <p>Impairs several monocyte and neutrophil functions of the innate immune system, including respiratory burst, chemotaxis, phagocytosis, and polarization<sup>18–21</sup></p> <p>Its inhibitory properties on human neutrophils and complement activation may be related to its lipid carrier vehicle<sup>18,22</sup></p> <p>At least partly inhibits human neutrophil chemotaxis by suppressing the p44/42 mitogen-activated protein kinase pathway<sup>18,20</sup></p> <p>Has proliferative-suppressing effects in polymorphonuclear leukocytes of critically ill patients who are primarily immunosuppressed<sup>23</sup></p> <p>Reduces extracellular IL-8 accumulation by diminishing its secretion from polymorphonuclear leukocytes, despite constantly high intracellular levels and mRNA expression of IL-8<sup>15</sup></p> <p>Binds to 5-lipoxygenase and attenuates leukotriene B<sub>4</sub> production<sup>24</sup></p> <p>Produces only cell-mediated immunomodulatory effects on innate immunity that might be generated by its lipid solvent<sup>18</sup></p> <p>Drug-specifically suppresses neutrophil function and reduces their phagocytic capacity<sup>25–27</sup></p> <p>Reduces the phagocytotic capacity of alveolar macrophages and increases their gene expression of pro-inflammatory cytokines (IL-1b, IL-8, IFN-<math>\gamma</math>, and TNF-<math>\alpha</math>)<sup>28,29</sup></p> <p>Long-chain triglyceride-diluted propofol inhibits neutrophil superoxide production, reduces the burst activity of neutrophils, and inhibits phagocytosis<sup>21,25–27</sup></p> <p>Long-/medium-chain triglyceride-diluted propofol raises the burst activity of neutrophils<sup>30</sup></p> <p>Reduces the intracellular calcium concentration in neutrophils<sup>21</sup></p> <p>Chemically resembles the chain-breaking antioxidant <math>\alpha</math>-tocopherol due to its phenolic hydroxyl group, exerting antioxidant properties<sup>31</sup></p>
Ketamine	<p>Inhibition of transcription factor activator protein-1 and NF-<math>\kappa</math>B<sup>32</sup></p> <p>Decreases the production of CRP, TNF-<math>\alpha</math>, and IL-6<sup>33–35</sup></p> <p>Attenuates lipopolysaccharide-induced liver injury by reducing cyclooxygenase-2, inducible nitric oxide synthase, and NF-<math>\kappa</math>B binding activity<sup>33,34,36</sup></p>

Table II. (Continued)

Agent	Immunomodulation
Etomidate	<p>Exerts suppressive effects on the adhesion-molecule expression and oxygen-radical production of human neutrophils<sup>37</sup></p> <p>Suppresses monocyte chemotaxis<sup>12</sup></p> <p>The preparation with long-/medium-chain triglycerides increases the respiratory burst activity of polymorphonuclears<sup>26,30</sup></p> <p>Mediates its suppressive effects on polymorphonuclear function by changing cellular amino acid turnover<sup>38</sup></p> <p>Increases the prevalence of nonresponsiveness to corticotropin in patients with septic shock<sup>39</sup></p> <p>Suppresses adrenal function, even as a single dose, and increases the possibility of pro-inflammatory cytokine production and secondary infections<sup>40–47</sup></p> <p>A single dose of etomidate is associated with increased acute respiratory distress syndrome and multiple organ dysfunction syndrome partly due to an effect of etomidate on the inflammatory response (ie, inhibition of 11<math>\beta</math>-hydroxylase)<sup>48–51</sup></p>
Dexmedetomidine	<p>Increases the risk for inflammatory organ injury in trauma patients<sup>52</sup></p> <p>Is associated with increased inflammatory response and worsening of respiratory function<sup>53</sup></p> <p>Reduces pro-inflammatory cytokine levels in septic and critically ill patients<sup>18,54,55</sup></p> <p>Significantly decreases leukocyte count, CRP, IL-6, IL-8, and TNF-<math>\alpha</math> levels<sup>18,54</sup></p> <p>Suppresses the biological behavior of HK-2 cells treated with lipopolysaccharide by down-regulating ALKBH5<sup>56</sup></p> <p>Dexmedetomidine preconditioning protects cardiomyocytes against hypoxia/reoxygenation-induced necroptosis by inhibiting high-mobility group box 1-mediated inflammation<sup>57</sup></p> <p>Protects against high-mobility group box 1-induced cellular injury by inhibiting proptosis<sup>58</sup></p> <p>Preemptive administration of dexmedetomidine increases the activity of cervical vagus nerve and has the ability to successfully improve survival in experimental endotoxemia by inhibiting inflammatory cytokine release through <math>\alpha_7</math>nAChR-dependent mechanism<sup>59</sup></p> <p>Enhances resolution of high mobility group box 1 protein-induced inflammation through a vagomimetic action<sup>60</sup></p>
Opioids	<p>Different opioids affect immune function differently, depending on drug factors, host factors, and the duration of exposure<sup>61</sup></p> <p>Morphine, fentanyl, remifentanyl, methadone, and codeine present strong immunomodulatory effects<sup>62</sup></p> <p>Tramadol, hydrocodone, oxycodone, and buprenorphine present much weaker or no immunomodulatory capacity<sup>62</sup></p> <p>Opioids that cross the blood-brain barrier exert more immunomodulatory effects than do opioids that do not cross it<sup>63</sup></p> <p>Can cause direct sympathetic nervous activation, which may suppress the proliferation and function of some immune cell populations and primary and secondary lymphoid tissues<sup>64</sup></p> <p>Acute administration of opioids results in either a reduction or no change in adrenocorticotrophic hormone or glucocorticoids<sup>9,62</sup></p>

(continued on next page)

Table II. (Continued)

Agent	Immunomodulation
Rocuronium	<p>Attenuate the circadian rhythm of adrenocorticotrophic hormone and cortisol, leading to consistent increments in circulating levels of these hormones, which might be sufficient to produce immune suppression<sup>62</sup></p> <p>Impair monocyte and neutrophil function, NK cell—mediated cytotoxicity, lymphocyte and macrophage proliferation, and cytokine release<sup>9,62,65,66</sup></p> <p>Promote apoptosis by direct activation of the enzymes involved in cell apoptosis (mainly morphine)<sup>9,62</sup></p> <p>Inhibit leukocyte function by increasing intracellular concentrations of nitric oxide and cyclic adenosine monophosphate, and by inhibiting NF-κB via nitric oxide—dependent mechanisms<sup>9,62</sup></p> <p>Enhance NK cell cytotoxicity and increase NK and cytotoxic (CD<sup>8+</sup>) cell counts (mainly fentanyl)<sup>18,65</sup></p> <p>Produce inhibitory effects on leukocyte migration, NK cell activity, and mitogen-induced lymphocyte proliferation (mainly sufentanil and alfentanil)<sup>18,54,67</sup></p> <p>Modulates cytokine production by macrophages/monocytes during the stress response<sup>19,59,62</sup></p> <p>Inhibits apoptosis<sup>18,54</sup></p> <p>Exerts central sympatholytic effects, including stimulation of cholinergic anti-inflammatory pathways<sup>18,54</sup></p> <p>Has antinociceptive action involving interactions between pain and immune factors (pro-inflammatory cytokines)<sup>18,54</sup></p> <p>Inhibits inflammation and pain by suppressing nitric oxide production and enhancing prostaglandin E2 synthesis in endothelial cells<sup>68</sup></p>
Cisatracurium	<p>Decreases the plasma levels of TNF-α and IL-6 by inhibition of nicotinic acetylcholine receptor-α1 in lung injury<sup>69</sup></p> <p>Decreases pulmonary concentrations of IL-1β, IL-6, and IL-8 and serum concentrations of IL-1β and IL-6 in acute respiratory distress syndrome<sup>70–72</sup></p> <p>Decreases the expression of high-mobility group box-1 in lung tissues and CD<sup>4+</sup> and CD<sup>8+</sup> in T-lymphocyte subsets<sup>73</sup></p> <p>Decreases the expression of TNF-α, IL-6, and high-mobility group box-1 in serum, as well as an alleviation of high-mobility group box-1 protein expression in the diaphragm in early stages of sepsis<sup>74</sup></p> <p>Decreases total IgE<sup>75</sup></p>
Succinylcholine	<p>Decreases the number of total lymphocytes, total IgE, and CD4/CD8 fractions<sup>75</sup></p> <p>Increases fatty acid—binding protein, insulin, IL-1b, prolactin, S100, calcium-binding protein B, and TNF-α when administered with methohexital<sup>76</sup></p>

ALKBH = alkylated DNA-repair protein alkB homolog; CRP = C-reactive protein; Hif = hypoxia-inducible factor; HK = hexokinase; IFN = interferon; Ig = immunoglobulin; IL = interleukin; nAChR = nicotinic acetylcholine receptor; NF-κB = nuclear factor κB; NK = natural killer; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

However, these combinations must be further evaluated in well-conducted trials.

Interestingly, EETs appear to affect other organs as well. In the renal cortex, EETs selectively oppose V1 receptor-mediated vasoconstriction, contributing to the relative insensitivity of medullary blood flow to V1-receptor activation. The vasculature of the injured kidney has an impaired vasodilatory response in critically ill patients and loses its autoregulatory behavior.<sup>94</sup> Consequently, EETs may have renoprotective effects, which is of great importance considering the increased prevalence of acute kidney injury in patients with COVID-19.<sup>95</sup>

Several EETs have also been associated with improvement in the recovery of contractile function in isolated perfused mouse hearts<sup>96</sup> subjected to global ischemia and reperfusion, and with a reduction in infarct size in intact canine, rat, and mouse hearts.<sup>97</sup> Of note, the cardioprotective effects of various EETs are the result of activation of the  $\delta$ -opioid receptor by the release of the  $\delta$ -active peptide Met-enkephalin.<sup>98</sup> Also, in hypoxic and hemodynamically unstable patients, an increased level of hypoxia-inducible factor  $1\alpha$  may play a role in cardioprotection mediated by EET analogue EET-B in reperfusion.<sup>99,100</sup> Evidence that the  $\kappa$ -opioid receptor may mediate part of the EET effect,<sup>101</sup> while EETs and opioids are acting on similar signaling pathways, comes from the pre- and postconditioning field. All of these findings indicate that the role of opioid receptors in patients with COVID-19 is multifaceted and must be further investigated.<sup>98</sup>

Inhibition of the development of severe inflammation and the enhancement of inflammation resolution by anesthetics may be a promising alternative approach to limiting severe organ damage and improving outcomes in patients with COVID-19.<sup>102</sup> Based on current evidence, midazolam, propofol, ketamine, dexmedetomidine, opioids, rocuronium, cisatracurium, and succinylcholine may have favorable immunomodulatory effects when used in the induction or maintenance of anesthesia. However, etomidate may be harmful, and its use may be questionable.

### Potent Effects of Etomidate in Patients with COVID-19

Etomidate is a short-acting IV anesthetic agent used for emergency anesthesia, and for years it has been a

drug of choice in RSI and endotracheal intubation.<sup>103</sup> Etomidate is a carboxylated imidazole ( $C_{14}H_{16}N_2O_2$ ) that binds at a distinct binding site associated with a  $Cl^-$  ionophore at the  $\gamma$ -aminobutyric acid  $A$  receptor. Binding at a distinct site increases the duration for which the  $Cl^-$  ionophore is open and prolongs the postsynaptic inhibitory effect of  $\gamma$ -aminobutyric acid in the thalamus.

### Adrenocortical Inhibition

It is believed that etomidate does not compromise sympathetic tone or myocardial function and produces minimal hemodynamic changes after induction.<sup>104</sup> Nonetheless, the advantage of its hemodynamic stability and the disadvantage of its adrenocortical inhibition are not well-proved due to a lack of adequately powered randomized, controlled trials. To date, much of the evidence has been based on systematic reviews and retrospective studies.

In 2008, the results from CORTICUS (Hydrocortisone Therapy for Patients With Septic Shock),<sup>105</sup> a multicenter, randomized, double-blind, placebo-controlled trial, suggested that etomidate may prolong the reversal of shock or reduce the likelihood of reversal of shock, raising serious concerns about the use of etomidate in cases of septic shock. Another study reported that etomidate treatment was associated with an increased prevalence of nonresponsiveness to corticotropin in patients with septic shock, with hydrocortisone administration having no effect on outcome in these patients.<sup>39</sup> In 2010, Hohl et al<sup>40</sup> conducted a systematic review of the effects of a single bolus dose of etomidate on cortisol levels and mortality. The investigators concluded that etomidate suppressed adrenal function transiently. However, whether the suppression of the adrenal function had a significant effect on mortality remained unclear. Two years later, Chan et al<sup>41</sup> evaluated the effects of a single dose of etomidate on mortality in patients with severe sepsis and septic shock. Despite the existence of possible bias, that meta-analysis reported a statistically significant association between a single dose of etomidate for RSI and mortality, which persisted even after a second sensitivity analysis. Nonetheless, another systematic review and meta-analysis, published in 2015,<sup>46</sup> reported no significant correlation between etomidate and mortality in patients with sepsis. The same year, however, a



Cochrane database systematic review<sup>42</sup> reported that, although there was no conclusive evidence of increases in mortality or health care resource utilization with etomidate use in critically ill patients, the use of etomidate seemed to have increased the risk for adrenal gland dysfunction and multiorgan dysfunction syndrome (MODS). In clinical practice, while etomidate may have fallen from favor over the past 5–10 years because of its effects on adrenal hormone levels affecting adrenoceptor function, it remains an important tool for RSI.

### **Immunomodulatory Effects**

In 2009, Warner et al<sup>48</sup> analyzed the data from a clinical trial of prehospital hypertonic saline administration in severely ill trauma patients and reported that a single dose of etomidate for RSI was associated with increased prevalences of ARDS and MODS, partly due to an effect of etomidate on the inflammatory response (ie, inhibition of 11 $\beta$ -hydroxylase). However, apart from the decrease in adrenocortical function and cortisol levels for up to 72 h after a single dose,<sup>49</sup> the use of etomidate may be associated with other, more insidious, unintended effects.

The first evidence of the association of etomidate with “late death” was reported in a study in trauma patients conducted in 1983.<sup>52</sup> Twenty years later, a retrospective analysis reported that etomidate use was associated with an increased risk for inflammatory organ injury, with patients with an APACHE score of >20 exerting the higher risk for adrenal suppression, ARDS, or MODS.<sup>48</sup> This finding was further supported by the results of a substudy of the data from HYPOLYTE (Etomidate Increases Susceptibility to Pneumonia in Trauma Patients),<sup>50</sup> a multicenter, randomized, double-blind, placebo-controlled trial of hydrocortisone in trauma patients, which reported that etomidate use was an independent risk factor for hospital-acquired pneumonia on day 28. In a study of the association of etomidate use with mortality in critically ill patients, the investigators reported that etomidate administration was associated with a trend toward a relative increase in mortality.<sup>51</sup> However, the small increase in relative risk reported in the literature until 2013 may have been an underestimate, given that some of the previous trials had been underpowered to detect it. In 2014, Hinkewich and Green<sup>106</sup>

reported an absolute increase in 28-day mortality of 9.2% in trauma patients who received etomidate. Although the difference in mortality was nonsignificant after adjustment for covariates, the investigators stated that the data showed a trend toward increased mortality, advocating that etomidate should be used with caution.

The latest evidence of the immunomodulatory effects of etomidate came out in October 2019, when the results of a planned secondary analysis of PROPPR (Pragmatic Randomized Optimal Platelet and Plasma Ratios),<sup>53</sup> a randomized, clinical trial, were reported at the 2019 annual meeting of the American Society of Anesthesiologists. The investigators compared data from patients whose anesthesia was induced with etomidate (n = 87) versus those who received other induction agents (n = 492). Blood samples were taken at admission and at 2, 4, 6, 12, and 24 h, and were screened for 27 cytokines by enzyme-linked immunosorbent assay. Comparison of 30-day clinical outcomes showed an association between etomidate and an increased rate of ARDS (32% vs 16%;  $P < 0.001$ ) and decreased ventilator-free days (18.5 vs 25 days;  $P < 0.05$ ). Hospital days, intensive care unit days, and mortality were unaffected ( $P = 0.33, 0.07, \text{ and } 0.70$ , respectively). The researchers concluded that the use of etomidate in the acute setting in trauma patients was associated with increased inflammatory response and worsening of respiratory function.

### **Should Etomidate Be Used in Patients With COVID-19?**

The evidence is alarming and may be extremely important for the management of critically ill patients with COVID-19, in whom the equilibrium of the inflammatory response appears to be a major determinant of survival. Moreover, etomidate has been reported to increase pro-inflammatory cytokine production *ex vivo* in whole-blood cell cultures challenged with lipopolysaccharide and could therefore prolong the systemic inflammatory response syndrome in patients with COVID-19,<sup>43</sup> increasing the possibility of secondary infections and corticosteroid dysfunction.<sup>44,45,107,108</sup> On the other hand, the etomidate-mediated decrease in cortisol concentration may decrease monocyte and neutrophil activity and the homing of DCs.<sup>109</sup> Furthermore, the decreased cortisol levels increase the risk for

inflammation-related complications, such as ARDS and MODS, by impairing the maintenance of vascular tone and endothelial integrity, enhancing the production of phospholipase A2, and impairing leukocyte apoptosis.<sup>110</sup> Also, low cortisol increases L-selectin and CD 11b expression on neutrophils and monocytes, which promote chemotaxis, migration of white blood cells, and tissue destruction.<sup>48</sup>

Another major issue is how etomidate and its possible impact on cytokine/inflammatory proliferation are affected by the concurrent use of corticosteroids. The potent suppression of adrenal function and the increase in pro-inflammatory cytokine production by etomidate typically results in reflex administration of exogenous hydrocortisone, with the goals of improving hemodynamics and suspending the exacerbation of lung injury and MODS (Figure 1). Some evidence suggests that corticosteroids may inhibit the immune response and pathogen clearance. Although septic shock was reported in 7 of 140 patients (5%) with 2019-nCoV included in published reports as of January 29, 2020, evidence then was insufficient for recommending corticosteroid treatment in patients with COVID-19 and ARDS.<sup>111</sup> As a result, the World Health Organization in March reported that corticosteroids should not be used in patients with 2019-nCoV–induced lung injury or shock, except in a subset of critically ill patients or in the setting of a clinical trial. However, a study published in May 2020 reported that most (70%) nonsurviving patients with COVID-19 had septic shock, which was significantly higher than the rate of shock in survivors.<sup>112</sup> Also, the recommendation in the recent Surviving Sepsis Campaign guideline is to use low-dose corticosteroid therapy (shock reversal), over no corticosteroid therapy, in mechanically ventilated adults with COVID-19 and ARDS (weak recommendation, low-quality evidence).<sup>113</sup> Understandably, there is a conflict due to the limited evidence, but the medical community may err toward enthusiasm with corticosteroids, given the profound inflammation. Based on the aforementioned, with etomidate administration, the use of other corticosteroids may be increased compared with the currently recommended dexamethasone, and well-tolerated alternatives, alone or in combination, should be used in RSI in patients with COVID-19.<sup>111,114,115</sup>

## CONCLUSIONS

To date, significant efforts have been made to draw the attention of anesthetists to the importance of appropriate precautions in providing RSI in patients with COVID-19. In this context, the anesthesia provider should keep in mind that a two-phase division is largely suspected in these patients: a first, immune defense–based, protective phase, in which the goal of treatment should be to boost the immune response; and a second, inflammation-driven, damaging phase, during which the immune response should probably be suppressed. Although the evidence regarding this deadly disease remains scarce, the data mentioned herein indicate that further immediate research is warranted for the full clarification of the effects of anesthetics in COVID-19. Considering that systemic inflammation and cytokine storm are associated with adverse outcomes, as well as that reduced inflammation may impair antimicrobial immunity, the authors highly recommend that clinicians monitor patients with COVID-19 receiving anesthetics with anti-inflammatory activity. Although the role of etomidate is questionable, caution in its use is recommended until more evidence is available. It is hoped that this article serves as a template for future explorations and catalyzes new direction toward improved outcomes in patients with COVID-19.

## DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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