

The Myth of Rescue Reversal in “Can’t Intubate, Can’t Ventilate” Scenarios

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BACKGROUND: An unanticipated difficult airway during induction of anesthesia can be a vexing problem. In the setting of can’t intubate, can’t ventilate (CICV), rapid recovery of spontaneous ventilation is a reasonable goal. The urgency of restoring ventilation is a function of how quickly a patient’s hemoglobin oxygen saturation decreases versus how much time is required for the effects of induction drugs to dissipate, namely the duration of unresponsiveness, ventilatory depression, and neuromuscular blockade. It has been suggested that prompt reversal of rocuronium-induced neuromuscular blockade with sugammadex will allow respiratory activity to recover before significant arterial desaturation. Using pharmacologic simulation, we compared the duration of unresponsiveness, ventilatory depression, and neuromuscular blockade in normal, obese, and morbidly obese body sizes in this life-threatening CICV scenario. We hypothesized that although neuromuscular function could be rapidly restored with sugammadex, significant arterial desaturation will occur before the recovery from unresponsiveness and/or central ventilatory depression in obese and morbidly obese body sizes.

METHODS: We used published models to simulate the duration of unresponsiveness and ventilatory depression using a common induction technique with predicted rates of oxygen desaturation in various size patients and explored to what degree rapid reversal of rocuronium-induced neuromuscular blockade with sugammadex might improve the return of spontaneous ventilation in CICV situations.

RESULTS: Our simulations showed that the duration of neuromuscular blockade was longer with 1.0 mg/kg succinylcholine than with 1.2 mg/kg rocuronium followed 3 minutes later by 16 mg/kg sugammadex (10.0 vs 4.5 minutes). Once rocuronium neuromuscular blockade was completely reversed with sugammadex, the duration of hemoglobin oxygen saturation >90%, loss of responsiveness, and intolerable ventilatory depression (a respiratory rate of ≤4 breaths/min) were dependent on the body habitus and duration of oxygen administration. There is a high probability of intolerable ventilatory depression that extends well beyond the time when oxygen saturation decreases <90%, especially in obese and morbidly obese patients. If ventilatory rescue is inadequate, oxygen desaturation will persist in the latter groups, despite full reversal of neuromuscular blockade. Depending on body habitus, the duration of intolerable ventilatory depression after sugammadex reversal may be as long as 15 minutes in 5% of individuals.

CONCLUSIONS: The clinical management of CICV should focus primarily on restoration of airway patency, oxygenation, and ventilation consistent with the American Society of Anesthesiologists’ practice guidelines for management of the difficult airway. Pharmacologic intervention cannot be relied upon to rescue patients in a CICV crisis. (Anesth Analg 2016;XXX:00–00)

After the introduction of sugammadex into clinical practice, it has been suggested that in cases in which a rapid sequence intubation is indicated, administration of rocuronium followed shortly thereafter

by large-dose sugammadex is a safer alternative than the use of conventional doses of succinylcholine for reestablishing neuromuscular activity in “can’t intubate, can’t ventilate” (CICV) situations.¹ The onset of effect of rocuronium 1.2 mg/kg is not different from that achieved by 1.0 mg/kg of succinylcholine.² When this dose of rocuronium is followed 3 minutes later by the administration of 16 mg/kg of sugammadex, the total duration of neuromuscular block is shorter by 4 to 5 minutes than what is observed after an “intubating dose” of succinylcholine.³ Because 90% twitch recovery at the adductor pollicis occurs in approximately 6 minutes after rocuronium/sugammadex administration and presumably functional diaphragm activity returns even sooner, it has been hypothesized that respiratory activity will recover before significant arterial desaturation.⁴⁻⁶

However, as a 2012 editorial comment has pointed out, in the first few minutes after induction of anesthesia, the primary factor determining return of spontaneous respiration may not be the depth of neuromuscular block but rather the degree of centrally mediated respiratory depression

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induced by the opioids and hypnotics used for the induction of anesthesia.^{7,8}

Unfortunately, clinical investigations of the duration of apnea after commonly used induction regimens are surprisingly few. Comparative studies are almost nonexistent. The search for the optimal induction sequence (adequate reflex suppression plus rapid recovery) is complicated by the number of possible alternatives. In view of the complexity and cost of doing a comprehensive comparative clinical study, it is unlikely that any such investigation will be forthcoming. An alternative approach is to use pharmacology simulation models in an attempt to address these questions. We hypothesized that in a patient with an obstructed airway in the immediate postinduction period, "rescue reversal" of neuromuscular blockade would not guarantee a clinically useful reduction in the period of vulnerability (i.e., pharmacological approaches are not appropriate as the first line of managing CICV situations).

The aim of this study was to compare, by computer simulation, the duration of unresponsiveness and ventilatory depression by the use of a common induction technique with predicted rates of oxygen desaturation in various size patients and explore to what degree rapid reversal of neuromuscular blockade with sugammadex might improve the return of spontaneous ventilation.

METHODS

Simulation

Using common induction agents, 3 sets of simulations were performed to predict (1) onset and duration of unresponsiveness and ventilatory depression; (2) onset, duration, and reversal of neuromuscular blockade; and (3) the rate of oxygen desaturation in the presence of apnea for selected body sizes and ventilatory variables (inspired oxygen, respiratory rate, and alveolar tidal volume). Table 1 presents the patient demographics of various body sizes, and Table 2

Table 1. Simulated Patient Demographics

Age: 40 y
Gender: male
Height: 170 cm
Weights, kg
75 (BMI = 26 kg/m ²)
95 (BMI = 33 kg/m ²)
130 (BMI = 45 kg/m ²)

BMI = body mass index.

Table 2. Dosing Regimen and Pharmacokinetic Models Used for Simulation

Drug and dose	Pharmacokinetic model	Weight scalar
Opioids		
Fentanyl 2 µg/kg	Shafer et al. ⁹	MFFM
Sedative hypnotic		
Propofol 2 mg/kg	Cortinez et al. ¹⁰	MFFM
Neuromuscular blocker		
Succinylcholine 1 mg/kg	Roy et al. ¹¹	TBW
Rocuronium 1.2 mg/kg	Kleijn et al. ¹²	TBW
Neuromuscular reversal agent		
Sugammadex 16 mg/kg	Kleijn et al. ¹²	TBW

MFFM = Modified fat-free mass; TBW = total body weight.

presents the induction agents, dose, and pharmacokinetic models used in these simulations. Pharmacokinetic simulations were used to predict effect-site concentrations over time for each drug presented in Table 2 as dosed.

Weight Scalars

When administering induction agents to obese individuals, clinicians often use a weight that results in a total dose that is less than what would be administered if using total body weight. Researchers have explored the use of *weight scalars* (e.g., ideal body weight, lean body mass, fat-free mass, pharmacokinetic mass, modified fat-free mass, etc.) with varied results. Several weight scalars use both height and weight whereas others use only height to predict a useful dosing weight. Samples of selected weight scalars for the patient demographics used in this simulation are presented in Table 3. The optimal weight scalar is not well defined for obese and morbidly obese patients and is likely different for individual sedatives, opioids, or neuromuscular-blocking agents. For simulation purposes, modified fat-free mass was used for propofol and opioids, and total body weight was used for neuromuscular-blocking agents and sugammadex. From a clinical perspective, the resultant total dose using these weight scalars was considered appropriate in patients with the body mass indexes (BMIs) reported in Table 1.

Simulations of Sedative and Analgesic Effects

To predict the effects from coadministration of propofol and an opioid, pharmacodynamic interaction models were used to estimate the probability of loss of responsiveness and ventilatory depression over time (Table 4). Predicted propofol and opioid effect-site concentrations from pharmacokinetic simulations were used as input into the interaction models. Model predictions of loss of responsiveness were defined as a loss to painful (trapezius squeeze) stimuli as defined by the modified observers assessment of alertness/sedation scale <2.¹⁵ Model predictions of ventilatory depression were defined as a respiratory rate of ≤4 breaths/min.^{14,16} Interaction models were built from observations in volunteers receiving propofol and remifentanyl in an unstimulated state. Relative opioid potency equivalencies were used to scale remifentanyl-propofol interaction models to fentanyl. Fentanyl effect-site concentrations were converted

Table 3. Dosing Weights for Selected Weight Scalars and Total Doses for Propofol and Fentanyl Using Those Weight Scalars

Weight scalar	Dosing weight, kg	Propofol 2 mg/kg, mg	Fentanyl 2 µg/kg, µg
Ideal body weight			
75 kg (BMI = 26 kg/m ²)	66	132	132
95 kg (BMI = 33 kg/m ²)	66	132	132
130 kg (BMI = 45 kg/m ²)	66	132	132
Fat-free mass			
75 kg (BMI = 26 kg/m ²)	57	113	113
95 kg (BMI = 33 kg/m ²)	65	129	129
130 kg (BMI = 45 kg/m ²)	74	147	147
Modified fat-free mass			
75 kg (BMI = 26 kg/m ²)	64	128	128
95 kg (BMI = 33 kg/m ²)	78	155	155
130 kg (BMI = 45 kg/m ²)	96	192	192

BMI = body mass index.

to equivalent remifentanyl effect-site concentrations using a relative potency of remifentanyl to fentanyl = 1:1.2.^{17,18}

Simulations of Neuromuscular Blockade and Reversal with Sugammadex

Predictions of effect-site concentrations and drug effect for rocuronium and reversal with sugammadex were made with the use of published pharmacokinetic and pharmacodynamic interaction models.¹² Pharmacokinetic models for rocuronium and sugammadex accounted for age and used allometric scaling to account for size in model parameter predictions. Predictions of effect-site concentrations and drug effect for succinylcholine were made with published pharmacokinetic and pharmacodynamic models.¹¹ Propofol and opioids do not alter the potency of neuromuscular-blocking drugs.^{19,20} Muscle relaxants were administered 1 minute after propofol was administered. Time to 50% recovery of the first twitch (T1) was used to compare the duration of effect between succinylcholine and rocuronium followed by reversal with sugammadex.

Simulations of Hemoglobin Oxygen Desaturation

To predict the time until the onset of oxygen desaturation, a system of equations (Supplemental Digital Content, Supplemental Table A, <http://links.lww.com/AA/B423>) was used to estimate the changes in alveolar oxygen

concentration and predicted hemoglobin oxygen saturation (SpO₂) during preoxygenation, induction of anesthesia, and subsequent apnea. The system of equations accounted for storage of oxygen in the functional residual capacity (FRC) as well as oxygen consumption throughout the period of modeled predictions. The equations used allometric scaling to account for height and weight in model parameters. The time until onset of oxygen desaturation was predicted for 2 periods of preoxygenation (1 and 3 minutes) for each of the 3 body sizes. The onset of oxygen desaturation was defined as SpO₂ of 90%. A list of assumptions and limitations of the simulations is presented in the Supplemental Digital Content (Supplemental Table B, <http://links.lww.com/AA/B423>). Elements of these assumptions include the following: The fraction of inspired oxygen (F_{IO₂}) was set to 0.6 to mimic a poor facemask seal and/or an uncooperative patient when attempting preoxygenation with an F_{IO₂} of 1. The respiratory rate was 14 breaths/min in an unstimulated awake individual. The resting alveolar tidal volume set at 3 mL/kg represented the anatomic dead space volume subtracted from the total tidal volume.

To compare the extent of desaturation between body sizes, the area under the curve (AUC) of hemoglobin oxygen saturation levels <90% was estimated. The AUC was defined as the integral of the hemoglobin oxygen saturation <90% over time. An example of the AUC estimation is presented in Figure 1. This set of simulations assumed a 3-minute period of preoxygenation with an F_{IO₂} of 0.6. Graphic representation of the AUC was used to compare values among body sizes.

An additional set of simulations was performed to explore the influence of changes in alveolar tidal volume, inspired oxygen concentrations, and respiratory rate on the time course of hemoglobin oxygen saturation. Alveolar tidal volume was varied over a range of 1 to 5 mL/kg in increments of 1 mL/kg. Inspired oxygen concentration was varied over a range of 0.2 to 1.0 in increments of 0.2. Respiratory rate was varied over a range of 4 to 16 breaths/min in increments of 4 breaths/min.

Simulation Comparisons

Comparisons of the duration of predicted effects were made to explore which effects persisted more than others after reversal of rocuronium with sugammadex and whether those

Table 4. Pharmacodynamic Interaction Models Used for Simulation		
Drug effect	Definition	Interaction model
Opioid sedative		
Loss of responsiveness ^a	OAA/S <2	Kern et al. ¹³
Ventilatory depression	Spontaneous ventilatory rate of ≤4 breaths/min	LaPierre et al. ¹⁴
Rocuronium-sugammadex		
Neuromuscular blockade reversal	Return of normal neuromuscular function	Kleijn et al. ¹²

An OAA/S <2 indicates no response to painful stimuli. OAA/S = Observer's Assessment of Alertness/Sedation. ^aNo model of consciousness or awareness exists; only models of responsiveness.

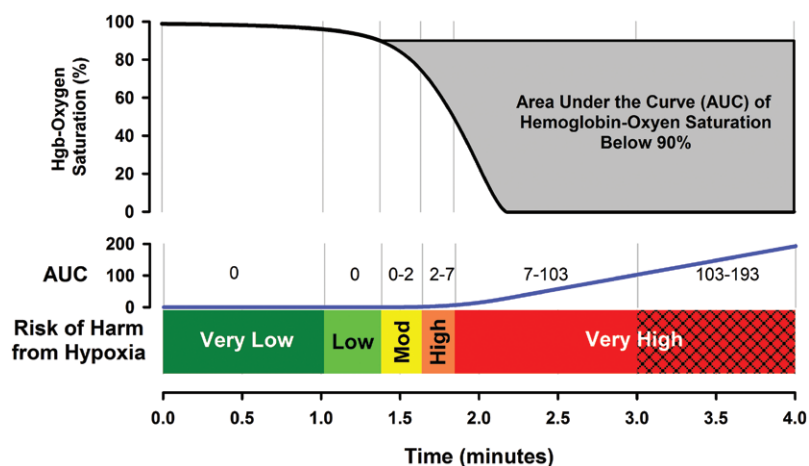


Figure 1. An example of model predictions of hemoglobin (Hgb) oxygen desaturation during a 4-minute period to illustrate (1) the area under the curve (AUC) of hemoglobin oxygen saturation levels <90% (gray area), (2) the change in AUC over time (blue line), and (3) a 5-point scale describing the potential risk of harm from hypoxia. This example assumes complete apnea during the 4-minute period. The cumulative AUC at each transition in the scale is presented as a numeric range within the AUC plot. The “very high” element of the scale has 2 segments: Solid red represents the duration of hemoglobin oxygen saturation <50 for up to 1.2 minutes. Cross-hatched red represents the period beyond 1.2 minutes and for simulation purposes is defined as a critical period associated with a very high risk of harm from hypoxic.

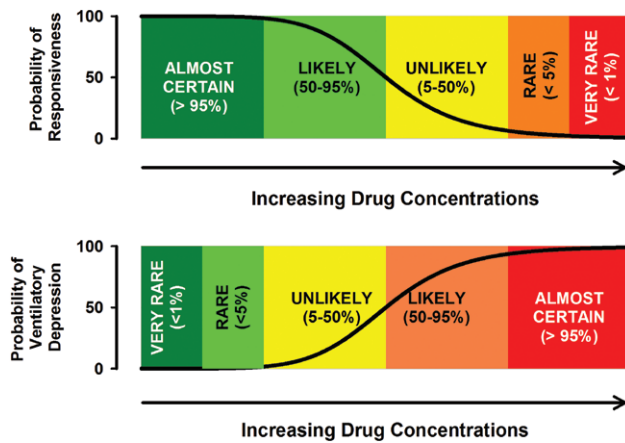


Figure 2. Five-point scale of model predictions of responsiveness and intolerable ventilatory depression. The black line represents the probability of effect with increasing effect-site concentrations of propofol combined with fentanyl.

effects would last longer than the duration of oxygen saturation >90%. Specific comparisons included the following:

1. The duration of neuromuscular blockade with 1.0 mg/kg succinylcholine vs 1.2 mg/kg rocuronium reversed 3 minutes later with 16 mg/kg sugammadex.
2. The duration of unresponsiveness and intolerable ventilatory depression (a respiratory rate of ≤ 4 breaths/min) after reversal of rocuronium for each body size and dosing regimen.
3. The duration of oxygen saturation >90% after reversal of rocuronium for each body size across a range of respiratory rates, inspired oxygen concentrations, and alveolar tidal volumes during preoxygenation.

To facilitate comparison between body sizes, a scale was used to provide a clinical interpretation of model predictions of responsiveness and intolerable ventilatory depression (Fig. 2). The probabilities of responsiveness and intolerable ventilatory depression were characterized by the use of a 5-point scale ranging from “very rare” to “almost certain.” To characterize the potential risk of an adverse event (i.e., anoxic brain injury or death) in the setting of an unanticipated difficult airway, inability to mask ventilate, failure to secure the airway, and rapid hemoglobin oxygen desaturation, interpretations of these scales were made using the following assumptions:

1. If unresponsive, yet spontaneously breathing, the likelihood of an adverse event is low. This scenario was defined as the probability of responsiveness is <50% corresponding to scale values of “unlikely,” “rare,” or “very rare,” yet the probability of tolerable ventilatory depression is <5% (“rare” or “very rare”).
2. If responsive, yet ventilatory depression is substantial, the likelihood of an adverse event is also low if a prompt to breathe provides a means of self-rescue. This scenario was defined as a probability or responsiveness >50% (“likely” to “almost certain”) with a probability of intolerable ventilatory depression is <5% (“rare” to “very rare”).
3. If unresponsive and with profound ventilatory depression, self-rescue will be ineffective, and the risk of harm from hypoxia is high.

Table 5. Scale Assignments According to the Changes in Hemoglobin Oxygen Saturation

Risk of patient harm	Drop in hemoglobin oxygen saturation, %
Very low	>95
Low risk	95–90
Moderate	90–75
High risk	75–50
Very high	<50

A 5-point scale was used to characterize the potential risk of harm from hypoxia (Fig. 1). Assignment of each category within the scale was based on the authors’ clinical experience, assuming a rapid desaturation in the presence of persistent apnea (Table 5). Additional assumptions were that a small decrease in saturation <95% has a “very low” or “low” risk of harm but is a precursor to more worrisome saturation changes. Once <90%, desaturation will accelerate over the next 30 to 60 seconds, leading to a change in risk from “moderate” to “very high” of potential harm from hypoxia. For saturations that persist <50% for longer than 1 to 2 minutes, a patient is in a critical condition with a very high risk of harm from hypoxia.

For comparison purposes in the context of predictions of responsiveness, intolerable ventilatory depression, and hypoxia, the following were used to estimate the periods of *high risk of hypoxic injury* after induction with failure to ventilate or secure the airway:

1. The probability of responsiveness <50% (“unlikely,” “rare,” or “very rare”),
2. The probability of intolerable ventilatory depression >5% (“unlikely,” “likely,” or “almost certain”), and
3. The predicted risk of harm from hypoxia is “high” or “very high.”

All 3 conditions were required to be considered a *high risk of hypoxic injury*. The time course of predictions was compared in graphical form by body size. Time segments that met these 3 criteria were identified.

RESULTS

Simulations

The time course of predicted plasma and effect-site concentrations after induction with propofol, fentanyl, and succinylcholine or rocuronium followed by sugammadex are presented in Figure 3 for 3 body sizes (BMI of 26, 33, and 45 kg/m²). The time course of predicted effects (responsiveness, ventilatory depression, and neuromuscular blockade) is also presented in Figure 3. The time course of lung oxygen stores and hemoglobin oxygen saturations after 1 and 3 minutes of preoxygenation also is presented in Figure 3.

The duration of neuromuscular blockade was longer with 1.0 mg/kg succinylcholine than with 1.2 mg/kg rocuronium followed 3 minutes later by 16 mg/kg sugammadex (10.0 vs 4.5 minutes). At the time of complete recovery from rocuronium-induced neuromuscular block to a train-of-4 ratio >0.9, there is a probability that 95% of patients who received succinylcholine are still completely paralyzed.

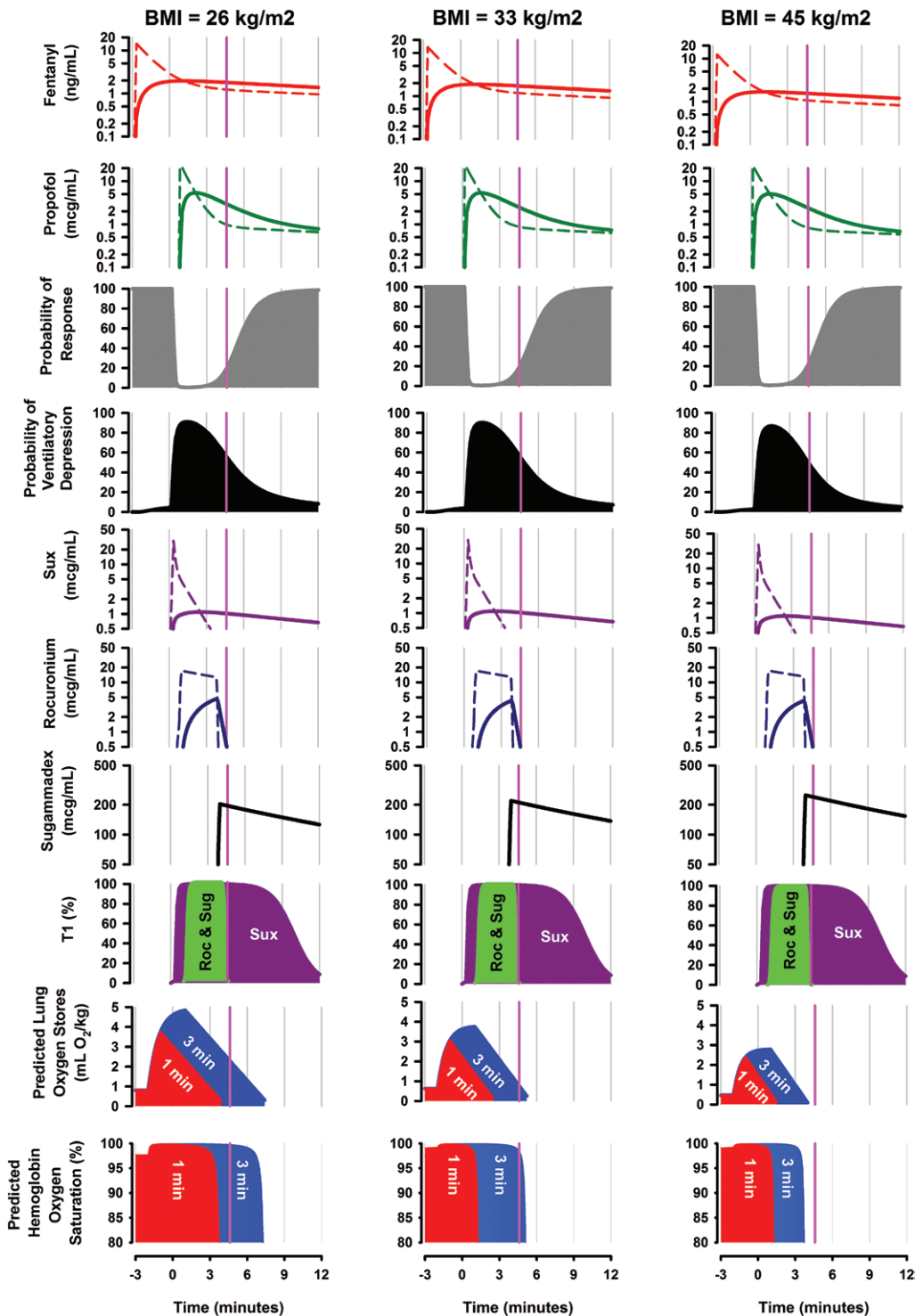


Figure 3. Predicted onset and duration of selected drug effects administered to a normal (body mass index [BMI] = 26 kg/m²), obese (BMI = 33 kg/m²), and morbidly obese (BMI = 45 kg/m²) individuals. Induction drug sequence was fentanyl followed 3 minutes later by propofol followed by either succinylcholine or rocuronium. Relaxants were administered 1 min after propofol administration. Time = 0 minutes is defined as the time propofol was administered. Rocuronium was reversed 3 minutes later with sugammadex. Doses of each drug are presented in Table 2. Predicted effects include probability of response based on the Observer's Assessment of Alertness/Sedation (OAA/S) scale,¹⁵ probability of ventilatory depression defined as a respiratory rate of ≤ 4 breaths/min in an unstimulated state, neuromuscular blockade is defined as probability of the first twitch depression (T1%) in patients who received succinylcholine or rocuronium/sugammadex paradigm and predicted hemoglobin oxygen saturation in the presence of apnea. The solid lines represent plasma concentrations. The dashed lines represent the effect-site concentrations. Predicted oxygen saturation (SpO₂) is presented as a function of the duration of preoxygenation before drug induced apnea. Red and blue represent 1 and 3 minutes of preoxygenation with an FiO₂ of 0.6, a respiratory rate of 14 breaths/min, and an alveolar tidal volume of 3 mL/kg. Alveolar tidal volume is defined as the anatomic dead space volume subtracted from the tidal volume. The pink vertical lines represent the time points at which neuromuscular blockade is completely reversed with sugammadex.

Once rocuronium neuromuscular blockade was completely reversed with sugammadex (marked with a vertical pink line in Fig. 3), the duration of hemoglobin oxygen saturation >90%, loss of responsiveness, and intolerable ventilatory depression were calculated and are presented in Table 6 across body sizes and duration of preoxygenation. After 1 minute of preoxygenation for obese and morbidly obese body sizes, hemoglobin oxygen saturation decreased <90% before reversal with sugammadex had taken place. With normal body habitus, desaturation <90% occurred

Table 6. Predictions of Duration of Effects Once Neuromuscular Blockade with Rocuronium Was Reversed with Sugammadex^a

BMI	One minute of preoxygenation	Three minutes of preoxygenation
	Duration of hemoglobin oxygen saturation >90% after complete reversal of neuromuscular blockade (min) ^b	
26 kg/m ²	c	2.6
33 kg/m ²	c	0.5
45 kg/m ²	c	c
Return of responsiveness (min)		
	50% of subjects recovered	95% of subjects recovered
26 kg/m ²	0.9	4.1
33 kg/m ²	1.0	4.2
45 kg/m ²	1.0	3.6
Return of spontaneous ventilation (min)		
	50% of subjects recovered	95% of subjects recovered
26 kg/m ²	0.4	11.2
33 kg/m ²	0.4	10.2
45 kg/m ²	0.0	7.9

BMI = body mass index.

^aFor discussion purposes, the duration of effects presented in this table are presented as the time from reversal of rocuronium neuromuscular blockade with sugammadex (vertical pink line in Fig. 3) until selected endpoints in drug effects. These include the probability of response based on the Observer's Assessment of Alertness/Sedation scale¹⁵ and the probability of ventilatory depression defined as a respiratory rate of ≤4 breaths/min in an unstimulated state. The reversal with sugammadex was assumed to be of equal duration for all body sizes.

^bAssumes that apnea persists despite full reversal of rocuronium with sugammadex until either ventilatory depression and/or unresponsiveness dissipates.

^cIndicates that the hemoglobin oxygen saturation is already <90%.

within the first minute of neuromuscular recovery. After 3 minutes of preoxygenation, the hemoglobin oxygen saturation also decreased <90% for the morbidly obese body size before neuromuscular recovery. In the obese body size, the hemoglobin oxygen saturation decreased <90% at the time of neuromuscular recovery, and the normal body size remained >90% for over a minute after reversal.

Using simulated data presented in Figure 3, a comparison of the AUC of hemoglobin oxygen saturation <90% vs time by body size is presented in Figure 4. The AUCs at 8 minutes were 193, 314, and 442 saturation %-minutes for BMIs of 26, 33, and 45 kg/m², respectively.

After neuromuscular blockade reversal, the duration of loss of responsiveness is relatively short. It predicts that half of the patients will be responsive in 1 to 2 minutes or less for all body sizes. Similarly, the time required for 19 of 20 patients to be responsive is 3 to 4 minutes across all body sizes. On the basis of the estimates of the duration of oxygen saturation >90% after 1 minute of preoxygenation, these simulations indicate that obese and morbidly obese patients may become hypoxic before becoming responsive. After 3 minutes of preoxygenation, however, only the morbidly obese patients may develop hypoxia before becoming responsive.

After neuromuscular blockade reversal, the time required for half of the patients to have a respiratory rate of ≤4 breaths/min is ≤1 minute for the morbidly obese; however, the time required that 1 of 20 patients will have a respiratory rate of ≤4 breaths/min after reversal may be as long as 12 minutes in 5% of individuals across all body sizes.

These simulations predict that after 1 or 3 minutes of preoxygenation, a majority of patients will likely have minimal ventilatory depression, but a small percentage will not. Ventilatory depression may persist for several minutes after oxygen saturation decreases <90%. Time windows meeting the 3 conditions of unresponsiveness, ventilatory depression, and a hypoxia for *high risk of hypoxic injury* after induction with failure to ventilate or secure the airway were identified in the 33 and 45 kg/m² body sizes and are presented in Figure 5. For a BMI of 33 kg/m², the duration was 1.5 minutes starting shortly after reversal with sugammadex

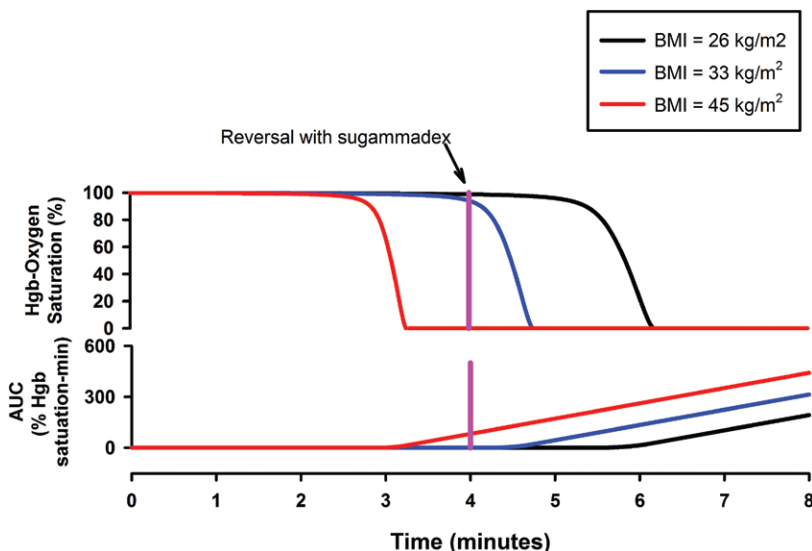


Figure 4. A comparison of hemoglobin (Hgb) oxygen saturations (top plot) and area under the curve (AUC) for saturations <90% over time (bottom plot) for 3 body sizes using simulated data presented in Figure 3. The saturation versus time predictions assumed 3 minutes of preoxygenation with an Fio₂ of 0.6 (before time = 0 minutes). Time 0 represents the induction time. The vertical pink line represents the time point at which neuromuscular blockade was reversed with sugammadex (4 minutes after induction with propofol). This timing mimicked the scenario of preoxygenation, followed by induction of anesthesia, onset of apnea (time = 0 minutes), administration of a neuromuscular-blocking agent at time = 1 minute, and reversal of neuromuscular blockade at time = 4 minutes.

and ending once the probability of responsiveness rose >50% ("likely"). For a BMI of 45 kg/m², the duration is 3 minutes. The onset of hypoxia (saturation <90%) occurs 1.5 minutes before reversal with sugammadex (time = 0 minutes). Once neuromuscular blockade is reversed, the risk of hypoxic injury persists for another 1.5 minutes until the probability of responsiveness increases >50%.

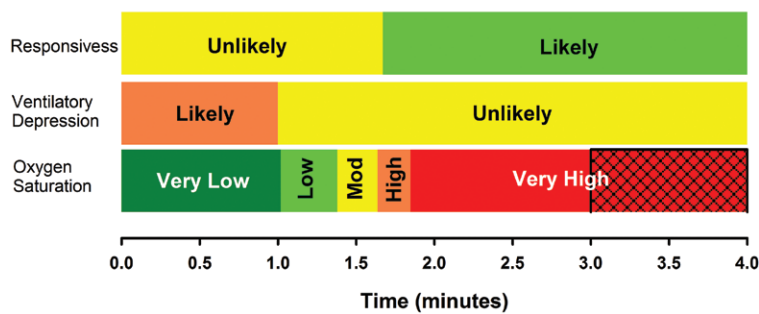
Simulations exploring how differences in respiratory rate (4–16 breaths/min), inspired oxygen concentration (F_IO₂, 0.2–1.0), and alveolar tidal volume (1–5 mL/kg) during 3 minutes of preoxygenation influence the duration of hemoglobin oxygen saturation >90% after apnea are presented in Figure 4. Differences in the inspired oxygen concentration had the largest impact that diminished with increasing BMI. The change in time to 90% hemoglobin oxygen saturation with a change in F_IO₂ from 0.2 to 1 was 10.5, 7.2, and 5.1 minutes for a BMI of 26, 33, and 45, respectively. The impact of

respiratory rate and alveolar tidal volume on the duration of hemoglobin oxygen saturation >90% was minimal except at low respiratory rates (4 breaths/min) or low alveolar tidal volumes (1 mL/kg).

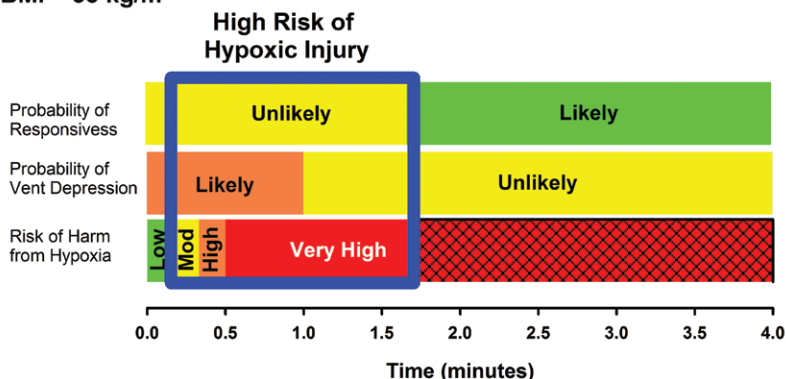
DISCUSSION

In this report, we compared, through simulation, the duration of unresponsiveness to painful stimuli and intolerable ventilatory depression (respiratory rate of ≤4 breaths/min) using a common induction technique with predicted rates of hemoglobin oxygen desaturation in various size patients and explored how rapid reversal of neuromuscular blockade with sugammadex improves return of spontaneous ventilation. Our hypothesis was that although reversal of rocuronium neuromuscular blockade with sugammadex would be very rapid, effects from propofol in combination with fentanyl, that render a patient unresponsive, with intolerable

BMI = 26 kg/m²



BMI = 33 kg/m²



BMI = 45 kg/m²

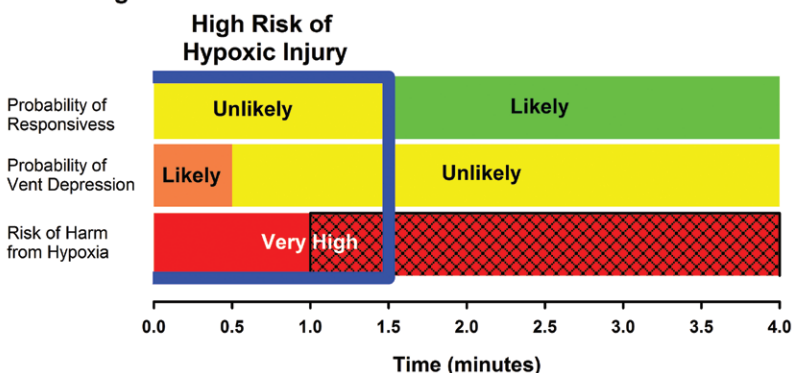


Figure 5. Comparison of responsiveness, intolerable ventilatory depression, and hypoxia to estimate periods of *high risk of hypoxic injury* after induction with failure to ventilate or secure the airway. For discussion purposes, the duration of effects presented in this table are presented as the time from reversal of rocuronium neuromuscular blockade with sugammadex (vertical pink line in Fig. 3) until selected end points in drug effects. See Methods for criteria used to estimate a high risk of hypoxic injury. Figures 1 and 2 present the definitions of the scales used to characterize the probability of effects. Time segments that met criteria are identified with a blue rectangle. The blue rectangle for the body mass index (BMI) of 45 kg/m² is truncated at time = 0 minutes because criteria were met for a high risk of injury 1.5 minutes before reversal with sugammadex.

ventilatory depression, or both, would persist longer than hemoglobin oxygen saturation would remain >90%.

After reversal of rocuronium with sugammadex, key findings of these simulations include the following: (1) return of neuromuscular function is quicker than with a standard dose of succinylcholine. (2) Oxygen saturation decreases <90% in <1 minute after 1 minute of preoxygenation and between 3 and 4 minutes after 3 minutes of preoxygenation in obese and morbidly obese patients. (3) Predictions of loss of responsiveness to painful stimuli revealed that the return of responsiveness nearly coincides with the onset of hemoglobin oxygen desaturation in obese and morbidly obese patients. (4) Predictions of intolerable ventilatory depression vary in duration based on BMI. The duration of intolerable ventilatory depression after reversal may be as long as 12 minutes in 5% of individuals regardless of the body habitus.

When interpreting the data presented in Figure 5 and Table 6, it is clear that the most dangerous conditions are when a patient has a loss of responsiveness and intolerable ventilatory depression where verbal and/or tactile stimuli encouraging the patient to take a deep breath is not feasible. Our simulations showed that there is a high probability of intolerable ventilatory depression that extends well beyond the time when oxygen saturation decreases <90%, especially in obese and morbidly obese patients. If ventilatory rescue is inadequate, oxygen desaturation will persist in this group, despite full reversal of neuromuscular blockade.

Attempting antagonism of the rocuronium-induced block with sugammadex is not always successful in restoring a patent airway and adequate ventilation and oxygenation in CICV situations.^{21,22} In addition, rescue reversal is not without attendant risks. Restoring diaphragmatic activities in the presence of an obstructed airway has the potential to result in a negative pressure pulmonary edema.²³ Furthermore, it takes time to prepare 16 mg/kg of sugammadex. A manikin study reported that in a CICV scenario, the time to calculate the correct dose of the drug and draw it up is 6.7 minutes.²⁴

As we have demonstrated in our simulations, rescue reversal in CICV situations does not guarantee the restoration of a patent airway and effective gas exchange.^{22,24} Reductions in the FRC and closing capacity (the oxygen reserves in the lungs) by approximately 20% occur shortly after induction of anesthesia in almost all patients.^{25,26} Greater reductions are seen during pregnancy, in obese and elderly persons, and in patients with chronic obstructive airway disease.²⁶⁻³⁰ Jense et al.³¹ concluded that "in morbidly obese patients, the time to desaturation is only long enough to allow a single attempt at intubation in an emergency situation." Furthermore, in a patient with an obstructed airway, the risk of desaturation in the immediate postinduction period is much greater in obese patients. Alveolar gas exchange during apnea (with a patent airway) entails both oxygen uptake and linear increase in mixed venous (and hence the alveolar) carbon dioxide tension.³² If the airway is occluded, the lung volume decreases by the difference between the oxygen uptake and the carbon dioxide output.

We wish to emphasize that the speed with which apparently very similar individual patients experience hemoglobin oxygen desaturation during apnea varies widely.³³⁻³⁵ In the absence of any neuromuscular-blocking drug, Naguib

et al.³⁵ demonstrated that 45% of young (mean age approximately 32 years), ASA physical status I subjects had arterial SpO_2 of <90% after an induction consisting of 2 $\mu\text{g}/\text{kg}$ fentanyl and 2 mg/kg propofol despite preoxygenation to an end-tidal oxygen concentration of >90%. Time to spontaneous diaphragmatic movement was reestablished after 2.7 ± 1.2 minutes (mean \pm SD). Benumof et al.³³ estimated in normal adults with 70 kg a best case time interval before 90% saturation was reached of 8 minutes. Heier et al.³⁴ found that ≥ 5 of 12 individuals had saturation <90% within 10 minutes. Similarly, Stefanutto et al.³⁶ demonstrated that an anesthetic induction consisting of propofol 2.0 mg/kg and remifentanyl 2.0 $\mu\text{g}/\text{kg}$ is likely to result in 6 ± 1 minutes (mean \pm SD) of apnea. In their study, SpO_2 decreased <80% in 4 of 12 volunteers. In contrast, when the opioid component of a propofol induction is reduced to alfentanil 10 $\mu\text{g}/\text{kg}$, Sørensen et al.⁴ present evidence in patients with normal body habitus that spontaneous respiratory efforts commence 3 minutes sooner after a rocuronium/sugammadex sequence than when succinylcholine is used to establish neuromuscular block. It appears that after the rocuronium/sugammadex paradigm, the ability to achieve rapid resumption of spontaneous ventilatory efforts is heavily dependent on the initial opioid administered and its dosage.

Anesthesiologists often lower their propofol and fentanyl weight-based doses in obese and morbidly obese patients. Dosing these drugs to total body weight can lead to unwanted adverse effects from high drug concentrations and/or prolonged effects. To mimic this reduced dosing behavior, we used a weight scalar, the modified fat-free mass, to formulate a proper dose for obese and morbidly obese individuals (Table 3). When we used this, our simulations led to similar predicted plasma and effect-site concentrations and drug effects in obese and morbidly obese individuals when compared with a lean individual.

For simulation purposes, we used total body weight for neuromuscular-blocking agents and sugammadex. This decision was based on published recommendations to dose succinylcholine to total body weight in obese and morbidly obese patients.³⁷ Total body weight also was used for rocuronium and sugammadex in this study. Although the pharmacokinetics of rocuronium appear not to be altered in obese patients,³⁸ in morbidly obese patients, the duration of action of rocuronium is significantly prolonged when it is dosed according to the total body weight.³⁹ Because sugammadex was used in adequate doses in these simulations, the choice of a specific weight scalar is not expected to affect the results.

Several assumptions were made regarding patient physiology and drug behavior that are difficult to consistently mimic through simulation. Interpatient variability and unique conditions can lead to markedly different outcomes. To explore the potential impact of changes in selected physiologic variables, we simulated how changes in respiratory rate, alveolar tidal volume, and inspired oxygen content influence the rate of hemoglobin oxygen desaturation. As illustrated in Figure 6, subtle changes in F_{IO_2} have a substantial effect, whereas changes in respiratory rate and alveolar tidal volume have smaller effects. This may be due to the diminishing influence of changes in the respiratory rate and alveolar tidal volume after 3 minutes of preoxygenation.

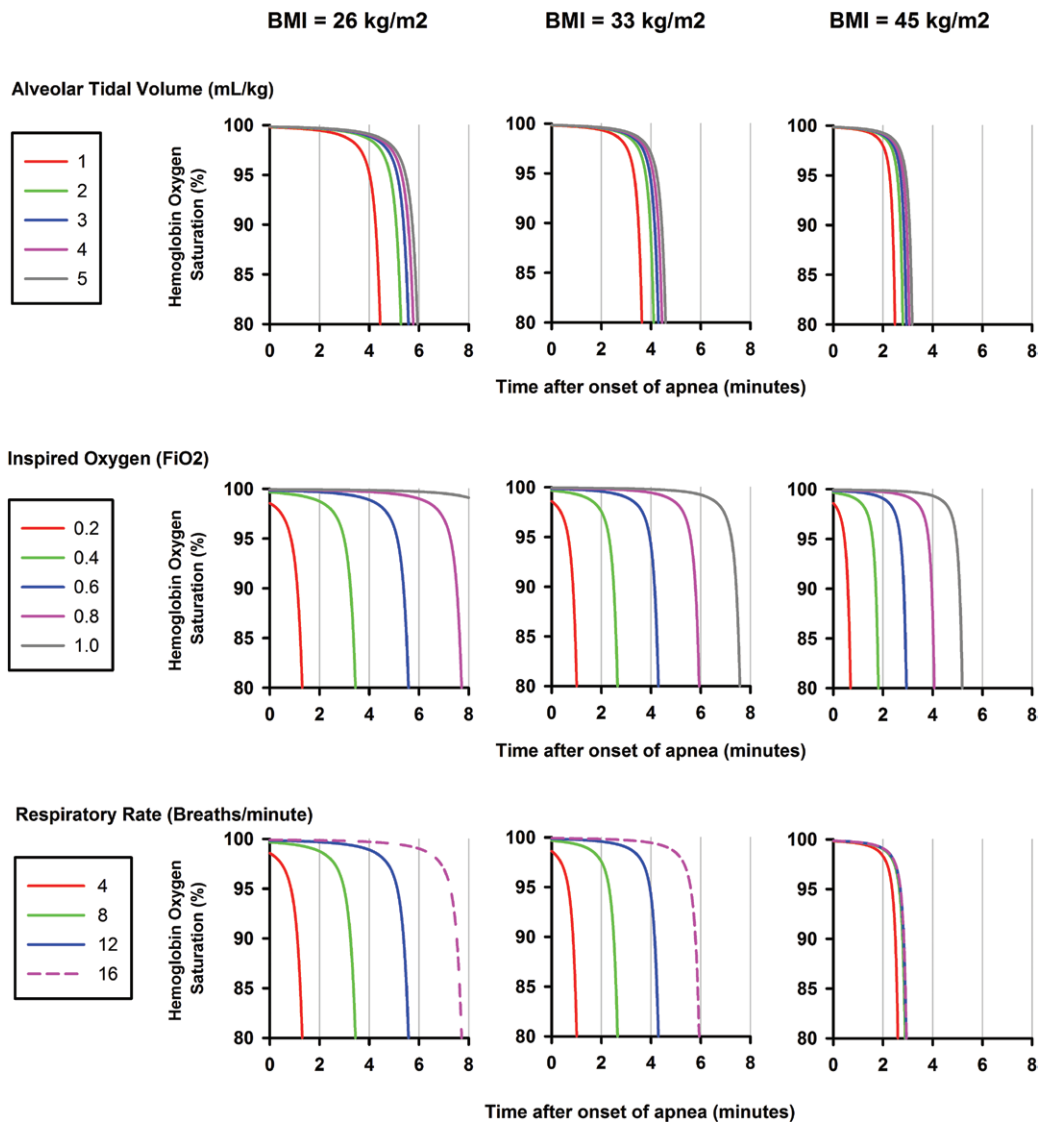


Figure 6. Simulations exploring how differences in respiratory rate (4–16 breaths/min), inspired oxygen concentration (fraction of inspired oxygen [FiO₂], 0.2–1.0), and alveolar tidal volume (1–5 mL/kg) during 3 minutes of preoxygenation influence the duration of hemoglobin oxygen saturation >90% after apnea for normal (body mass index [BMI] = 26 kg/m²), obese (BMI = 33 kg/m²), and morbidly obese (BMI = 45 kg/m²) individuals. If not otherwise stated, the respiratory rate was set to 14 breaths/min, the FiO₂ set to 0.6, and the alveolar tidal volume set to 3 mL/kg. Alveolar tidal volume was defined as the anatomic dead space volume subtracted from the tidal volume.

Although oxygen delivery to the FRC is reduced, enough oxygen is accumulated within 3 minutes to achieve denitrogenation. These physiologic variables are only a few among many that may substantially influence the predictions presented in our analysis.

Although our simulations provide a means of exploring an important clinical question, their accuracy in predicting individual patient behavior is limited. Farmery and Roe⁴⁰ have described a model of oxyhemoglobin desaturation in the apneic patient. We, however, have not considered the effects of apneic oxygenation (oxygen replacement on the assumption of an open glottis, and 100% inspired oxygen replacing loss of lung volume) in our simulations to have conservative estimates by omitting any delay in hypoxia that might occur from apneic oxygenation.

In summary, our simulations suggest that after induction of anesthesia, rescue reversal of rocuronium with sugammadex

in the setting of CICV may not render a patient responsive or provide immediate return to spontaneous ventilation, although it is a significant improvement over the duration of spontaneous neuromuscular blockade with succinylcholine. In fact, in obese and morbidly obese body sizes, even with preoxygenation, by the time reversal is accomplished; hemoglobin oxygen saturation is likely to be dangerously low. We believe that the clinical management of CICV should focus primarily on restoration of airway patency, oxygenation, and ventilation consistent with the American Society of Anesthesiologists' practice guidelines for management of the difficult airway.⁴¹ Pharmacologic intervention cannot be relied upon to rescue patients in a CICV crisis. ■

RECUSE NOTE

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REFERENCES

- Lee C. Goodbye suxamethonium! *Anaesthesia* 2009;64(suppl 1):73–81
- Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology* 1993;79:913–8
- Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. *Anesthesiology* 2009;110:1020–5
- Sørensen MK, Bretlau C, Gätke MR, Sørensen AM, Rasmussen LS. Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine: a randomized trial. *Br J Anaesth* 2012;108:682–9
- Barbosa FT, da Cunha RM. Reversal of profound neuromuscular blockade with sugammadex after failure of rapid sequence endotracheal intubation: a case report. *Rev Bras Anestesiol* 2012;62:281–4
- Desforges JC, McDonnell NJ. Sugammadex in the management of a failed intubation in a morbidly obese patient. *Anaesth Intensive Care* 2011;39:763–4
- Kopman AF, Kurata J. Can't intubate, can't ventilate: is "rescue reversal" a pipe-dream? *Anesth Analg* 2012;114:924–6
- Kopman AF, Kurata J. Rescue reversal: an addendum. *Anesth Analg* 2012;115:1254–5
- Shafer SL, Varvel JR, Aziz N, Scott JC. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *Anesthesiology* 1990;73:1091–102
- Cortínez LI, Anderson BJ, Penna A, Olivares L, Muñoz HR, Holford NH, Struys MM, Sepulveda P. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. *Br J Anaesth* 2010;105:448–56
- Roy JJ, Donati F, Boismenu D, Varin F. Concentration-effect relation of succinylcholine chloride during propofol anesthesia. *Anesthesiology* 2002;97:1082–92
- Kleijn HJ, Zollinger DP, van den Heuvel MW, Kerbusch T. Population pharmacokinetic-pharmacodynamic analysis for sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade. *Br J Clin Pharmacol* 2011;72:415–33
- Kern SE, Xie G, White JL, Egan TD. A response surface analysis of propofol-remifentanyl pharmacodynamic interaction in volunteers. *Anesthesiology* 2004;100:1373–81
- LaPierre CD, Johnson KB, Randall BR, White JL, Egan TD. An exploration of remifentanyl-propofol combinations that lead to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. *Anesth Analg* 2011;113:490–9
- Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990;10:244–51
- LaPierre CD, Johnson KB, Randall BR, Egan TD. A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy: implications on the time course of recovery. *Anesthesiology* 2012;117:252–62
- Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS, Glass PS. Reduction of isoflurane minimal alveolar concentration by remifentanyl. *Anesthesiology* 1996;85:721–8
- Westmoreland CL, Sebel PS, Gropper A. Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. *Anesth Analg* 1994;78:23–8
- McCarthy GJ, Mirakhor RK, Pandit SK. Lack of interaction between propofol and vecuronium. *Anesth Analg* 1992;75:536–8
- Khuenl-Brady KS, Agoston S, Miller RD. Interaction of ORG 9426 and some of the clinically used intravenous anaesthetic agents in the cat. *Acta Anaesthesiol Scand* 1992;36:260–3
- Kyle BC, Gaylard D, Riley RH. A persistent "can't intubate, can't oxygenate" crisis despite rocuronium reversal with sugammadex. *Anaesth Intensive Care* 2012;40:344–6
- Curtis R, Lomax S, Patel B. Use of sugammadex in a "can't intubate, can't ventilate" situation. *Br J Anaesth* 2012;108:612–4
- Suzuki M, Inagi T, Kikutani T, Mishima T, Bito H. Negative pressure pulmonary edema after reversing rocuronium-induced neuromuscular blockade by sugammadex. *Case Rep Anesthesiol* 2014;2014:135032
- Bisschops MM, Holleman C, Huitink JM. Can sugammadex save a patient in a simulated "cannot intubate, cannot ventilate" situation? *Anaesthesia* 2010;65:936–41
- Juno J, Marsh HM, Knopp TJ, Rehder K. Closing capacity in awake and anesthetized-paralyzed man. *J Appl Physiol Respir Environ Exerc Physiol* 1978;44:238–44
- Wahba RW. Perioperative functional residual capacity. *Can J Anaesth* 1991;38:384–400
- Damia G, Mascheroni D, Croci M, Tarenzi L. Perioperative changes in functional residual capacity in morbidly obese patients. *Br J Anaesth* 1988;60:574–8
- Baraka AS, Hanna MT, Jabbour SI, Nawfal MF, Sibai AA, Yazbeck VG, Khoury NI, Karam KS. Preoxygenation of pregnant and nonpregnant women in the head-up versus supine position. *Anesth Analg* 1992;75:757–9
- Wahba WM. Influence of aging on lung function—clinical significance of changes from age twenty. *Anesth Analg* 1983;62:764–76
- Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006;130:827–33
- Jense HG, Dubin SA, Silverstein PI, O'Leary-Escolas U. Effect of obesity on safe duration of apnea in anesthetized humans. *Anesth Analg* 1991;72:89–93
- Cherniack NS, Longobardo GS. Oxygen and carbon dioxide gas stores of the body. *Physiol Rev* 1970;50:196–243
- Benumof JL, Dagg R, Benumof R. Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. *Anesthesiology* 1997;87:979–82
- Heier T, Feiner JR, Lin J, Brown R, Caldwell JE. Hemoglobin desaturation after succinylcholine-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. *Anesthesiology* 2001;94:754–9

35. Naguib M, Samarkandi AH, Abdullah K, Riad W, Alharby SW. Succinylcholine dosage and apnea-induced hemoglobin desaturation in patients. *Anesthesiology* 2005;102:35–40
36. Stefanutto TB, Feiner J, Krombach J, Brown R, Caldwell JE. Hemoglobin desaturation after propofol/remifentanyl-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. *Anesth Analg* 2012;114:980–6
37. Lemmens HJ, Brodsky JB. The dose of succinylcholine in morbid obesity. *Anesth Analg* 2006;102:438–42
38. Pühringer FK, Keller C, Kleinsasser A, Giesinger S, Benzer A. Pharmacokinetics of rocuronium bromide in obese female patients. *Eur J Anaesthesiol* 1999;16:507–10
39. Leykin Y, Pellis T, Lucca M, Lomangino G, Marzano B, Gullo A. The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. *Anesth Analg* 2004;99:1086–9
40. Farmery AD, Roe PG. A model to describe the rate of oxyhaemoglobin desaturation during apnoea. *Br J Anaesth* 1996;76:284–91
41. Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, Hagberg CA, Caplan RA, Benumof JL, Berry FA, Blitt CD, Bode RH, Cheney FW, Connis RT, Guidry OF, Nickinovich DG, Ovassapian A; American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2013;118:251–70