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The Physiologically Difficult Airway and Management Considerations

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Abstract

Purpose of Review This paper evaluates the recent literature regarding the physiologically difficult airway.

Recent Findings Adverse events mainly desaturation, cardiovascular collapse, and cardiac arrest remain common complications. This risk is greatly increased in patients with altered physiology prior to intubation. Studies published over the last 5 years have explored many aspects surrounding the epidemiology, risks, and approach to managing the physiologically difficult airway.

Summary Important work has been done to identify directly modifiable risks of complications related to the physiologically difficult airway, but a large percentage of patients remain at high risk despite optimizing induction agents, preoxygenation, and first attempt success.

Keywords Physiologically difficult airway · Intubation · Preoxygenation · Cardiovascular collapse · Desaturation · Resuscitation

Introduction

The physiologically difficult airway was first described as a framework to explain the high rate of morbidity and mortality that occurs in critically ill patients despite one or few attempts, regardless of the presence or absence of any anatomic difficulty with tracheal intubation [1]. Underlying physiological abnormalities in these critically ill patients can increase vulnerability to the undesirable side effects of induction agents, attenuate or even eliminate the effectiveness of preoxygenation, and exaggerate the effects of cessation of spontaneous breathing and transition to positive pressure ventilation (Table 1).

Indirect signals of the physiologically difficult airway have been present for quite some time. In the seminal paper by Mort on the perils of repeated attempts, serious complications were far less frequent in patients with two or fewer attempts, but cardiovascular collapse and hypoxemia were still present in approximately 1 in 5 patients [2]. Sakles specifically evaluated the importance of first attempt success and reported that 1 in 6 patients experienced an adverse event despite first attempt success [3]. Jaber reported that patients in shock had a higher risk of complications despite the absence of a difficult airway [4]. Hypes published the first direct evidence of the risk of the physiologically difficult airway [5], where hypoxemia and hemodynamic instability were both associated with increased adjusted odds of a complication despite first attempt success, which occurred, again, in approximately 1 in 5 patients. Since we first described this conceptual framework in 2015, much work has been done to better understand and mitigate the risks imposed by physiologically difficult airways. Our last publication in this series reviewed the importance of and processes for preoxygenation and resuscitation and offered pragmatic recommendations for airway management in critically ill patients in general [6]. This paper focuses specifically on the physiologically difficult airway and summarizes the relevant airway management-related research published over the last 5 years.

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Table 1 Important abnormalities that increase the likelihood of a physiologically difficult airway

Risk	Effect	Key findings	Treatment	Comment
Hemodynamics	Poor contractility	Echocardiography: dilated LV, poor contractility on parasternal long axis view	Norepinephrine, add inotrope if still poor contractility	Avoid myocardial depressant induction agents
	Restrictive physiology	Echocardiography: hypertrophic LV myocardium, dilated left atrium, EA > 2, lateral mitral e' < 10 cm/s	Norepinephrine Fluid bolus (cautious) if LV appears volume responsive	Patients with advanced HFpEF can be extremely difficult when faced with a "second-hit" (e.g., sepsis), as ventriculoarterial uncoupling occurs easily with any change in preload or afterload
	Severe valvular abnormalities with hypotension	Echocardiography findings		
	Aortic stenosis	Thickened, poorly mobile, AV cusps, hypertrophic LV	Phenylephrine/vasopressin Norepi if poor EF Avoid tachycardia and maintain sinus rhythm Fluid bolus for preload	The severity of disease can be misleading when the LV starts to fail, reducing the gradient across the aortic valve
	Aortic regurgitation	Dilated LV, often poor EF, regurgitant color Doppler jet > 60% of LVOT	Norepinephrine/inotropes Avoid bradycardia Fluid bolus for preload if volume down	Hypertensive patients with aortic regurgitation (e.g., aortic dissection) require afterload reduction. Thus, the peri-intubation hemodynamics in these patients can be fragile and dynamic
	Mitral stenosis	Limited, no, or abnormal mitral leaflet movement, dilated left atrium, underfilled LV, dilated RV	Diuresis if RV is volume overload and concomitant RV failure, vasopressin, dobutamine/milrinone if poor EF (milrinone may be preferred), avoid tachycardia/dysrhythmia, avoid myocardial depression	This clinical condition is very tenuous. Under nonhypotensive conditions, the priorities are to avoid afterload reduction, increases in pulmonary artery pressures, and tachycardia. Hypotensive conditions are likely due to worsening RV failure. When possible, consider an awake intubation and potentially preintubation or early mechanical circulatory support
	Mitral regurgitation	Flail leaflets, dilated LA and LV hypertrophy if chronic, significant regurgitant color Doppler jet	Dobutamine, norepinephrine, preoxygenate with PEEP	Under nonhypotensive conditions, vasodilators can be helpful to promote forward flow
	Hemorrhage/hypovolemia	High systemic vascular resistance, narrow pulse pressure, relatively high diastolic pressure	Fluid bolus if volume responsive Norepinephrine inline	Prototypical condition is hemorrhagic shock. In hemorrhagic shock, blood product-based resuscitation is critical
	Vasoplegia	Low systemic vascular resistance, wide pulse pressure, relatively low diastolic pressure	Norepinephrine/vasopressin	Prototypical conditions include gram-negative sepsis and patients with cirrhosis. Avoid vasodilating induction agents
	Severe right ventricular dysfunction or failure	Echocardiography: Pressure and volume overloaded on parasternal short axis, dilated RA and IVC, TAPSE < 16 mm, S' < 10 cm/s, TAPSE/RVSP < 0.31	Fluid bolus if IVC collapsible, diuresis if dilated, norepinephrine/vasopressin, inhaled pulmonary vasodilators	Prototypical conditions are advanced pulmonary arterial hypertension and acute pulmonary emboli
	Hypertensive emergency	SBP > 180 mmHg and neurologic dysfunction	Vasodilators	Patients with acute intracranial emergencies are sensitive to an acute drop in cerebral perfusion pressure. Avoid using the induction agent as the blood pressure treatment

Table 1 (continued)

Risk	Effect	Key findings	Treatment	Comment
Hypoxemia	High work of breathing with acute hypoxemic respiratory failure	High respiratory effort per breath, respiratory rate > 30	Preoxygenate with noninvasive respiratory support to reduce work of breathing	Patients with ARDS and high work of breathing despite noninvasive respiratory support are at high risk of rapid desaturation from acute V/Q mismatch on induction
	High intrapulmonary shunt	Low PaO_2/FiO_2 or SpO_2/FiO_2 despite high oxygen concentration on noninvasive respiratory support	Inhaled nitric oxide	Consider awake intubation in patients with refractory hypoxemia
	Low functional residual capacity	Significant airspace disease, obesity, late term pregnancy, pleural effusions, hemothoraces	Preoxygenate with noninvasive respiratory support, drain extrapulmonary fluid/air collections, position optimally	
	Critical anemia	High cardiac output state with critically low hemoglobin and usually elevated lactate	Transfuse red blood cells Preoxygenate with noninvasive respiratory support given high work of breathing	Avoid myocardial depressant induction agents
Oxygen consumption	Increased consumption (e.g., thyroid storm)	High cardiac output state, tachycardia, atrial fibrillation	Fluid resuscitate, norepinephrine/vasopressin inline	Avoid myocardial depressant or vasodilating induction agents
	Decreased consumption (e.g., metabolic acidosis due to salicylate or metformin toxicity)	Profound metabolic acidosis, severe acidemia despite very high minute ventilation	Consider renal replacement therapy prior to intubation Bicarbonate use uncertain Vasopressin infusion prior to intubation given profound acidemia	Limit apnea time and match minute ventilation requirement as much as possible

LV left ventricle, *EA* ratio of E wave to A wave on mitral inflow velocities, *HFpEF* heart failure with preserved ejection fraction, *LVOT* left ventricular outflow tract, *EF* ejection fraction, *AV* aortic valve, *RV* right ventricle, *RA* right atrium, *PEEP* positive end-expiratory pressure, *IVC* inferior vena cava, *TAPSE* tricuspid annulus plane systolic excursion, *RVSP* right ventricular systolic pressure, *SBP* systolic blood pressure, *ARDS* acute respiratory distress syndrome, *V/Q* ventilation to perfusion ratio, PaO_2/FiO_2 ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen, SpO_2/FiO_2 ratio of oxygen saturation by pulse oximetry to fraction of inspired oxygen

Search Strategy

Recent publications between January 1, 2018, and January 1, 2024, were identified by literature search of the PubMed and Cochrane databases. The search terms included ("intubation"[Title/Abstract]) AND ("Critically Ill"[Title/Abstract]) and the following filters were applied: Clinical Trial, Meta-Analysis, Observational Study, Practice Guideline, Randomized Controlled Trial, and Systematic Review. Studies on neonates or pediatric patients ≤ 18 years, case reports, editorials, animal or manikin studies, and non-English language reports were excluded. The resulting titles and abstracts were reviewed for relevance (233 articles), and the full text was reviewed for all articles involving the physiologically difficult airway (41 articles). References from each selected article were reviewed for pertinent articles, and relevant new publications after the search date were manually included (17 additional articles), leaving 59 included articles.

Epidemiology

Studies published over the last 5 years that met inclusion criteria for this review have added further insight into the burden of the physiologically difficult airway. Two large recent registry studies from emergency department intubations showed that first attempt success may be preserved in the presence of anatomically difficult airway characteristics; however, first attempt success without adverse events is not. Both studies showed that the adjusted odds of first attempt success without an adverse event decreases in the presence of physiologically difficult airway characteristics, confirming the concept [7, 8]. De Jong evaluated risk factors associated with peri-intubation cardiac arrest using data collected from 1847 intubations performed during six randomized clinical trials or observational studies across 64 ICUs in France [9]. The cardiac arrest rate was 2.7%, while preintubation hypotension (systolic blood pressure < 90 mmHg), hypoxemia, absence of preoxygenation, a body mass index > 25 kg/m^2, and age > 75 years were associated with increased adjusted odds of peri-intubation cardiac arrest. Hypotension, hypoxemia, and the absence of preoxygenation had the strongest associations, and sensitivity analyses did not reveal a protective association with either first attempt success, ketamine use, or fluid loading. Furthermore, the increasing odds of cardiac arrest were more than linear with the addition of each risk factor (adjusted odds 1.31 for one risk factor and 9.89 for ≥ 4 risk factors). In 2020, the same group confirmed our findings of the importance of first attempt success and the high rate of complications despite first attempt success, but added further knowledge of the physiologically difficult airway by demonstrating the differences in complication rates by attempt [10]. They found that the rates of hypoxemia start high and increase linearly with each successive attempt, but the rates of cardiovascular collapse start high and stay flat with a trend toward decreasing by number of attempts. These findings were further supported by similar results in the subsequent International Observational Study to Understand the Impact and Best Practices of Airway Management in Critically Ill Patients (INTUBE) study [11••]. This study enrolled consecutive intubations in the ED or ICU over 8 weeks among nearly 200 hospitals across 29 countries and provides the first glimpse of widespread airway practices and complications in critically ill patients.

INTUBE reported other key insights from across the world. Nearly 40% of patients were on noninvasive respiratory support (noninvasive positive pressure ventilation [NIPPV], nasal high flow [NHF], or continuous positive airway pressure [CPAP]) prior to intubation, and nearly 30% had bilateral lung opacities on chest imaging, yet only 19% were preoxygenated with noninvasive respiratory support. One in four patients was on a vasopressor, while the mean heart rate and blood pressure were relatively normal. Propofol and midazolam were the most commonly used induction agents. Nearly half of the patients (45.2%) had a major adverse event, most commonly cardiovascular instability (42.6%), severe hypoxemia (9.3%), or cardiac arrest (3.1%). Among those who experienced a cardiac arrest, hemodynamic instability and hypoxemia were the most common causes. There were important differences in demographics between those who had a major adverse event and those who did not. Those with adverse events were more commonly sicker based on median Sequential Organ Failure Assessment (SOFA) score (8, interquartile range 5–11 vs 6, interquartile range 4–9), had comorbid New York Heart Class III or IV heart failure (11% vs 7%), had bilateral infiltrates (32% vs 25%) or pleural effusions (16% vs 11%), had worse oxygenation based on both the median PaO_2/FiO_2 (148, interquartile range 92–243, vs 182, interquartile range 110–287) and the median SpO_2/FiO_2 (150, interquartile range 100–233, vs 189, interquartile range 110–290), were more commonly on pressors (34% vs 19%) or received fluids (43% vs 33%), and tended to have lower mean blood pressure.

A systematic review and meta-analysis of major adverse events in critically ill patients, which included relevant studies until late 2022, found an overall major adverse event rate of 30.5%, but more adverse events occurred in the ICU (41%) than in the ED (17%) [12]. Their meta-analyses also revealed a correlation between hemodynamic instability before intubation and major adverse events, as well as the use of propofol as the induction agent. Respiratory failure as the indication for intubation, propofol as the induction agent, or using a muscle relaxant were all associated with a higher prevalence of hypoxemia. A higher mean heart rate prior to induction was associated with a higher cardiac arrest rate, while etomidate was associated with a lower incidence of cardiac arrest.

Smischney explored the risks of hypotension [13] and hypoxemia [14] using a multicenter prospective cohort registry. Their data provided a fairly granular insight into this concept, finding that preintubation hemodynamic status (hypotension defined as a mean arterial pressure < 65 mmHg, systolic pressure < 130 mmHg, sepsis diagnosis) and peri-intubation pharmacologic agents (diuresis in the preceding 24 h, vasopressors immediately prior to intubation or etomidate as the induction agent), age, and increasing severity of illness were all associated with postintubation hypotension [13], while noninvasive ventilation and difficult mask ventilation, emergency intubation, cardiac reasons for intubation, or fluid resuscitation were all associated with hypoxemia [14]. They developed the HYpotension Prediction Score (HYPS), which quantifies the relative weights and relationships between the associated variables for hypotension, with increasing scores associated with nonlinear increases in odds of hypotension [15]. A secondary analysis of the INTUBE study found similar variables associated with postintubation cardiovascular collapse, but they found that propofol as the induction agent was the only process-related modifiable factor, with the patient-related factors being age, heart rate, systolic blood pressure, and oxygen saturation [16].

In the original description of the physiologically difficult airway, we described severe right ventricular dysfunction or failure as an independent physiologically difficult airway phenotype independent of hemodynamic instability [1]. This was largely experiential and physiology-based, given the effects of airway management and its pharmacologic agents on right ventricular function; however, there were few data at the time. A recent study by Al-Saadi provided the first direct data on the risk of RV dysfunction as an independent risk factor for the physiologically difficult airway [17••]. Patients with moderate or severe RV dysfunction prior to intubation had increased adjusted odds of cardiac arrest or hemodynamic instability with intubation, as well as an association with mortality (moderate RV dysfunction odds ratios 2.65–4.14, depending on the model, severe—2.66–5.01 depending on the model).

Taken together, the findings in these studies support the notion that hypoxemia rates are a function of the adequacy and efficacy of preoxygenation [18, 19] and that cardiovascular collapse is a function of the underlying hemodynamic abnormalities exaggerated by induction agents and the transition to positive pressure ventilation.

The COVID-19 pandemic was an unprecedented time in modern medicine. Significant challenges were imposed on airway management, from concerns about aerosol transmission to patients lingering on noninvasive respiratory support past the point of failure to improve work of breathing and gas exchange. Cattin evaluated complication rates with intubation in COVID-19 patients in Italy between November 2020 and May 2021 [20]. Compared to INTUBE, their patient population was on average larger (BMI 30 vs 25), had a higher prevalence of hypertension (52% vs 40%), and more commonly had bilateral lung infiltrates on chest imaging (96% vs 28%). Nearly 40% of patients had a predicted anatomically difficult intubation. More patients were preoxygenated with noninvasive respiratory support (48% vs 19%), but fewer were on vasopressors (8% vs 26%) or received fluid boluses (19 vs 38%) prior to intubation. The first attempt success rate was 91%, and no patients had a difficult airway (> 2 attempts); however, 74% of patients had a major adverse event (severe hypoxemia 44%, hemodynamic instability 66%, cardiac arrest 2.8%), and 25% had more than one adverse event. Even with first attempt success, 68% of patients experienced an adverse event, and multivariable regression again demonstrated significant associations between preintubation physiologic abnormalities and complications. In the United States, a single-site study retrospectively compared complication rates between 782 intubations immediately prior to the start of the pandemic and 478 intubations in the early pandemic [21]. Patients were more likely to be intubated for hypoxemic respiratory failure during the pandemic (73% vs 28%). Despite using procedural modalities most likely to reduce complications (video laryngoscopy 89% vs 53%, neuromuscular blockade 86% vs 46%) by increasing first pass success (95% vs 83%), complication rates were nearly 100% higher (29.5% vs 15.2%) during the pandemic, mainly from desaturation. Despite almost fivefold greater adjusted odds of first attempt success during the pandemic from the increased use of RSI and VL, patients had an adjusted odds of 2.21 (1.5–3.4) of a major adverse event compared to patients intubated before the pandemic, with the major difference in patient demographics being more severe hypoxemia on average based on the SpO2/FiO2 before intubation (98 vs 313) and PaO2/FiO2 after intubation. Similar findings were reported from a prospective observational study of 1837 intubations across 43 Spanish ICUs [22]. Increased VL and NBMA use during the pandemic resulted in a higher first attempt success, but still had a high rate of hemodynamic instability (26.5%) and severe hypoxemia (20.3%).

Another key insight into the physiologically difficult airway was provided by Taboada in an observational study comparing intubating conditions in the operating room and the ICU. They evaluated all nonpregnant adult patients intubated using direct laryngoscopy in the ICU within a month of an elective intubation in the OR by the same group of anesthesiologists in both locations [23]. Demographics were fairly similar to INTUBE, and hemodynamically neutral induction agents (etomidate 67%, propofol 26%) and rapid onset paralytic agents (succinylcholine 90%, rocuronium 5%) were used more often in the ICU than in the OR (etomidate 31%, propofol 69%, succinylcholine 15%, rocuronium 29%, cisatracurium 55%). However, more patients had hypotension (28% versus 4%) or more hypoxemia (14% versus 2%) in the ICU locations, suggesting that, in the same group of patients with the same anatomy and intubated by the same group of experts in both locations, the underlying physiologic difficulties likely increased their risk.

Guidelines

Several recent guidelines now recognize the importance of preintubation physiology during airway management. The Difficult Airway Society guidelines for tracheal intubation in critically ill patients stress the importance of advanced preoxygenation and resuscitation in general [24]. The Society for Airway Management published the first guidelines specifically for the evaluation and management of the physiologically difficult airway, with more specific recommendations based on the underlying phenotype for a particular patient [25••]. The most recent Canadian Airway Focus Group [26] and American Society of Anesthesiologists [27] guidelines partially incorporate the physiologically difficult airway. Both guidelines recommend considering an awake intubation strategy for patients at risk of rapid desaturation, particularly when combined with potential anatomic difficulty. Finally, the Society of Critical Care Medicine guidelines for rapid sequence intubation were unable to make any strong recommendations regarding aspects of the physiologically difficult airway because of low, very low, or nonexistent evidence [28].

Devices

As the above epidemiological data demonstrate, there is an association between first attempt success and a reduction in major adverse events, and because video laryngoscopy is associated with increased first attempt success, there has been renewed focus on the optimal laryngoscope for RSI.

Hossfield conducted an observational study on 1006 consecutive intubations in an anesthesiologist-staffed helicopter emergency medical services unit in Germany [29]. In this study, a standard (Macintosh) geometry video laryngoscope was used with the monitor turned away from the operator to obtain a glottic view using direct laryngoscopy; then, the monitor was moved into view for a glottic view and intubation by video laryngoscopy. They found that video laryngoscopy significantly improved the glottic view, which was associated with a higher odds of first pass success (12.6, 6.70–23.65), even for experienced operators. Similar findings were reported in the ED setting [30].

Several debated aspects of video laryngoscopy have been explored in the last 5 years. First, while experience does make a difference in success rates, the learning curve is confirmed to be steep in the ICU [31], as has been previously shown in the ED [32]. Second, intubation is more successful when a stylet is used than when an endotracheal tube is inserted without a stylet [33]. Specifically, for video laryngoscopy, using a bougie (compared to a stylet) did not appear to improve first pass success in an unstructured environment [34], unlike in a structured environment [35]. Third, clinical trials comparing DL and VL over the last 5 years show improved first attempt success and safety profiles in the ED and ICU [36, 37••]. Systematic reviews and meta-analyses are mixed, with an early meta-analysis showing no difference [38] and the most recent one showing superiority of VL [39]. Finally, a recent Cochrane review also showed a favorable profile for VL over DL, even for the most experienced operators [40]. Given these findings, and the importance of first attempt success, a reasonable strategy is to routinely use video laryngoscopy when performing RSI, with a standard Macintosh geometry blade for intubations that are not predicted to be difficult and a hyperangulated geometry blade for intubations where anatomic difficulty is predicted.

While first attempt success is associated with significantly reducing airway-related morbidity and is the goal when performing RSI in critically ill patients, it is not completely protective for around 20% of patients. In those patients, more sophisticated peri-intubation resuscitation and preoxygenation strategies are required for those patients to tolerate RSI, and in some patients with refractory disease, a different airway management strategy may be required (e.g., an "awake" spontaneously breathing approach).

Preoxygenation and Apneic Oxygenation

One of the key findings in the epidemiology studies described above is the percentage of patients preoxygenated with a bag-valve mask (INTUBE 62% (11), Nauka 34% (21), Cattin 52% (20), Garnacho-Montero 76% (22)). Baillard evaluated this in a randomized clinical trial in critically ill patients with hypoxemic respiratory failure [41]. Patients were randomized to either preoxygenation with a bag-valve mask or noninvasive positive pressure ventilation for 3 min prior to induction. The study failed to show a difference in the primary outcome, maximum SOFA score within 7 days, but there were very informative secondary outcomes. Compared to a bag-valve mask, noninvasive ventilation resulted in fewer adverse events (17.8% vs 41.3%) and less desaturation < 80% (16.6% vs 41.3%).

High flow nasal oxygen is increasingly used for noninvasive respiratory support in patients with acute hypoxemic respiratory failure. Guitton compared high flow nasal oxygen to bag-valve mask for preoxygenation in patients without severe acute hypoxemic respiratory failure in a randomized clinical trial [42]. This trial also failed to show a difference in the primary outcome, the lowest oxygen saturation during intubation, but the results of the secondary outcomes are very informative. Despite patients preoxygenated with high flow nasal oxygen having more difficult intubations, as evidenced by more frequently requiring jaw thrust maneuvers (13% vs 33%), requiring more time (median 1 min [0.5–1.9] vs median 0.8 min [0.5–1.4]), a greater proportion taking > 10 min or 3 or more attempts (10% vs 1%), fewer patients had desaturation (12% vs 23%) and complications (6% vs 19%).

Compared to each other, randomized clinical trial data have shown no significant difference in severe hypoxemia between patients with acute hypoxemic respiratory failure preoxygenated with high flow nasal oxygen or noninvasive positive pressure ventilation [43]. However, a secondary analysis revealed that noninvasive positive pressure was associated with severe hypoxemia less frequently in patients with severe hypoxemia (24% vs 35%, adjusted odds ratio 0.56, 0.32–0.99). One key finding from these studies is the still high percentage, between 1 in 4 patients and 1 in 3 patients, that still have a severe desaturation despite advanced preoxygenation using either high flow nasal oxygen or noninvasive positive pressure ventilation.

Several studies have evaluated ways to further reduce this incidence for patients undergoing RSI. Removing the oxygen source before complete apnea results in a rapid loss of alveolar oxygen [44]. In a randomized clinical trial in which the majority of patients were preoxygenated with a bag-valve mask, a nonrebreathing mask, or a standard nasal cannula and only 20% were intubated for hypoxemic respiratory failure, mask ventilation between induction and laryngoscopy reduced the incidence of severe desaturation by half without an increase in aspiration [45]. A recent systematic review and meta-analysis of high flow nasal oxygen used for apneic oxygenation showed that apneic oxygenation has the greatest effect on reducing severe desaturation episodes in patients without significant hypoxemia, as determined by the PaO2/FiO2 ratio [46]. A secondary analysis of two clinical trials showed that mask ventilation between induction and laryngoscopy reduced severe desaturation episodes compared to apneic oxygenation with 15 L per minute [47]. However, there is only one comparison between mask ventilation and apneic oxygenation using a high flow nasal oxygen system [48]. In this study, patients with COVID-19 were intubated using a flexible endoscope after preoxygenation/apneic oxygenation with 50LPM HFNO or bag-valve mask, where HFNO reduced the incidence and depth of desaturation. The most recent Cochrane review on apneic oxygenation showed that there is unlikely a difference with apneic oxygenation [49]. A variation of apneic oxygenation using continuous noninvasive ventilation while nasally intubating with a flexible endoscope resulted in fewer desaturations < 80% (7.4% vs 37.7%) [50].

One of the major limitations in interpreting the literature on preoxygenation is that the assumption is that apnea with induction is the only option for airway management, thus the point of preoxygenation. However, some patients with acute hypoxemic respiratory failure are refractory to preoxygenation and perhaps these patients should be intubated while spontaneously breathing [1, 6, 18, 19, 25••, 51]. Kriege conducted a retrospective observational study evaluating the adverse events of an awake intubation approach compared to RSI in 135 critically ill patients intubated with a video or direct laryngoscope [52•]. They had an overall complication rate of 27%, but found a dramatically reduced complication rate in patients intubated with awake topicalization on high flow nasal oxygen (2.2%) compared to RSI (39%), even when accounting for level of experience.

A personalized approach to preoxygenation is provided in Fig. 1.

Hemodynamics

Several studies have evaluated various aspects of peri-intubation hemodynamics in the last 5 years. The pragmatic multicenter PrePARE trial evaluated the effect of initiating a 500 mL crystalloid bolus before induction [53]. They found no overall effect on the incidence of cardiovascular collapse, and the trial was stopped early for futility. However, they did find a trend toward benefit in patients receiving positive pressure ventilation either by preoxygenation by noninvasive ventilation or by bag-mask ventilation after induction. The follow-up trial in this patient population, PrePARE II, showed that initiating a fluid bolus prior to induction was not associated with a reduction in cardiovascular collapse [54].

A post hoc analysis of clinical trial data by the same group also suggested that prophylactic vasopressors were not associated with a reduction in cardiovascular collapse [55]. Interestingly, another study demonstrated that the use of push-dose vasopressors, including during intubation, increased blood pressure effectively but was associated with frequent medication dosing errors (11%) [56].

A very intriguing proof-of-concept study was conducted in which continuous transcutaneous CO_2 monitoring was evaluated during the peri-intubation period [57]. This study showed differences in transcutaneous CO_2 levels between preoxygenation methods and variability from preoxygenation through the first hours of mechanical ventilation. Most interestingly, they found an association between the rate of correction of CO_2 and the incidence of postintubation hypotension. While so much focus has been placed on modifiable

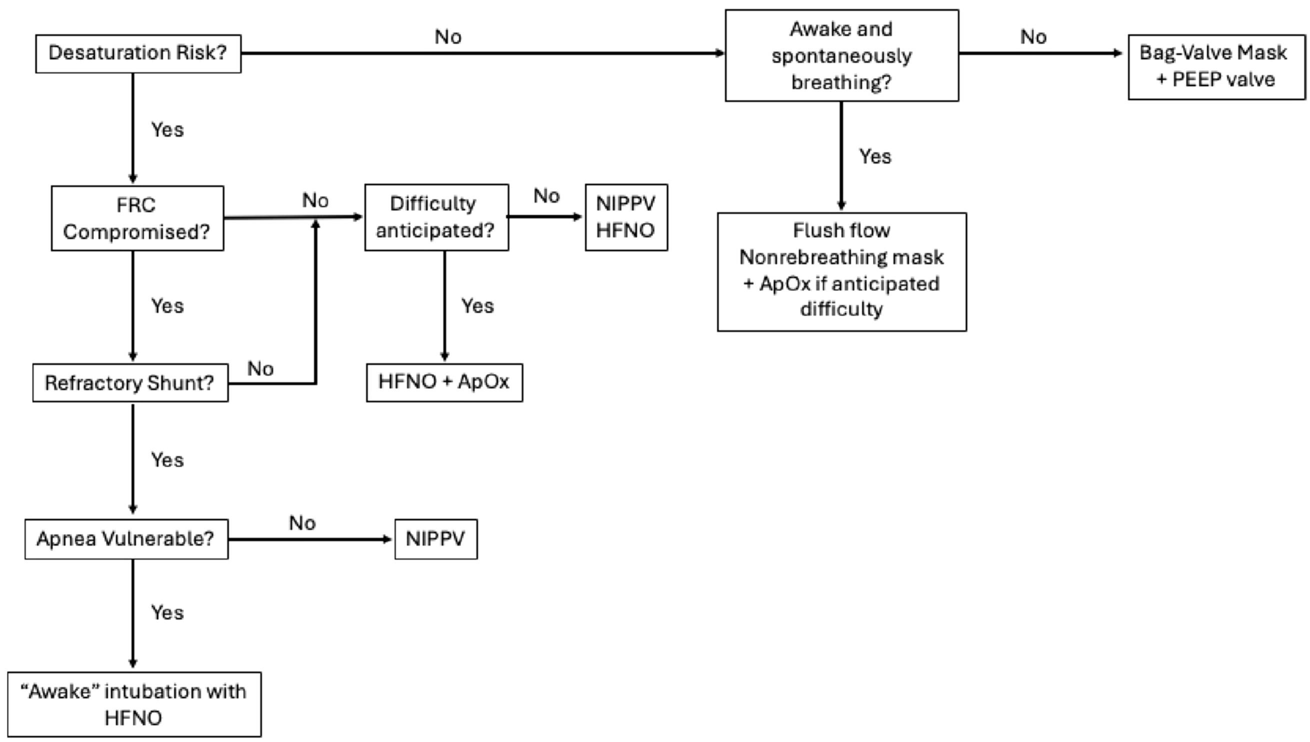

Fig. 1 Personalized preoxygenation. Preoxygenation requires a more personalized approach based on the specific underlying risk. For patients that are not at particularly high risk for desaturation, flush flow oxygen should be the standard as denitrogenation is generally the limiting step for preoxygenation effectiveness. Apneic oxygenation (ApOx) may be helpful for patients with anticipated difficulty. If patients are not spontaneously breathing, then preoxygenation with a bag-valve mask and positive end-expiratory pressure (PEEP) valve is the only realistic option. For patients at risk of desaturation, non-invasive positive pressure ventilation (NIPPV) and high flow nasal oxygen (HFNO) can be useful depending on the primary risk (i.e., reduced functional residual capacity (FRC) or intrapulmonary shunt refractory to denitrogenation and maximizing FRC). For patients with vulnerability to rapid desaturation with apnea, such as those with high respiratory effort in the setting of acute respiratory distress syndrome, an awake intubation approach with HFNO may be the best option

risks before intubation, this study highlights the potential importance of the fragility of hemodynamics immediately after the tube is placed.

Induction agents, particularly etomidate and ketamine, remain a priority area of interest in the literature. Observational studies have shown disparate outcomes, where ketamine is associated with both more frequent [58, 59], and less frequent [60], postintubation hypotension, or no difference compared to etomidate [61, 62]. Matchett conducted a randomized controlled trial comparing etomidate and ketamine in ICU patients and reported a greater 7-day mortality with etomidate but no difference in 28-day mortality, and secondary outcomes evaluating the hemodynamic effects of each all trended worse for ketamine [63]. A more recent trial also showed no difference in the maximum severity of illness, mortality, or postintubation incidence between the two [64]. Lastly, neither mixing ketamine and propofol [65] nor reducing the dose of etomidate appear to be associated with an overall reduction in postintubation hypotension [66•].

A systematic review and meta-analysis conducted by Kotani in 2023 concluded that there is a high probability of harm from etomidate [67]. However, there are major flaws in this meta-analysis that limit the interpretability. Among other limitations, the study analyzed the primary outcome of each of the included studies. This resulted in a nonstandard outcome, and if the outcome was standardized to 28-day mortality, the results change to nonsignificant.

Finally, another physiology study provided further insight into the hemodynamic effects and the magnitude of those effects with induction agents using a noninvasive cardiac output monitor [68]. This small study showed that in undifferentiated critically ill patients, propofol, ketamine, and etomidate had predictable effects on hemodynamics, but interestingly, they found that positive pressure ventilation after intubation only minimally affected hemodynamics.

Just like with preoxygenation, resuscitation requires a more sophisticated approach personalized to the individual patient's physiology. Figure 2 offers such a personalized approach.

Take-Home Messages

The 10 key principles learned over the last 5 years include the following:

1. The physiologically difficult airway imposes risk to patients that cannot be completely overcome by a single device, by the safety with first pass success, by imprecisely applied resuscitation, or by broadly applied induction agents.
2. Directly modifiable procedure-related risk factors for RSI include avoiding propofol as an induction agent, avoiding bag-mask ventilation for preoxygenation, and using video laryngoscopy routinely (standard geometry if anatomic difficulty is not predicted, hyperangulated if anatomic difficulty is predicted).
3. The complexity of acute hypoxemic respiratory failure and preoxygenation methods and the risk of adverse events remain a challenge. COVID-19-related studies particularly highlight the challenges with RSI in patients with hypoxemic respiratory failure.
4. Overall, too many patients are preoxygenated with bag-mask ventilation, and there is still too high of an incidence of desaturation in patients undergoing RSI in the setting of acute hypoxemic respiratory failure. Preoxygenation requires a more nuanced approach based on the underlying indication for intubation (Fig. 1).
5. Some patients with acute hypoxemic respiratory failure cannot be preoxygenated for RSI. In those patients, strongly consider an approach that maintains spontaneous breathing in patients with an appropriate mental status. This requires topicalization of the airway and minimal to no sedation. In patients where the mental status is not amenable to topicalization and cooperation with an awake approach, induction and early use of a second-generation supraglottic airway may improve oxygenation to facilitate laryngoscopy and intubation but more data are needed to inform this strategy.
6. Like preoxygenation, preintubation resuscitation requires a nuanced approach based on underlying physiology (Fig. 2). Imprecise fluid initiation and vasopressor administration are also unlikely to be successful when broadly applied.
7. Propofol, ketamine, and etomidate have all been shown to both improve and worsen hemodynamics in various studies. Propofol, however, is more consistently associated with risk across studies. Regardless, relying on largely indirect hemodynamic effects of an induction

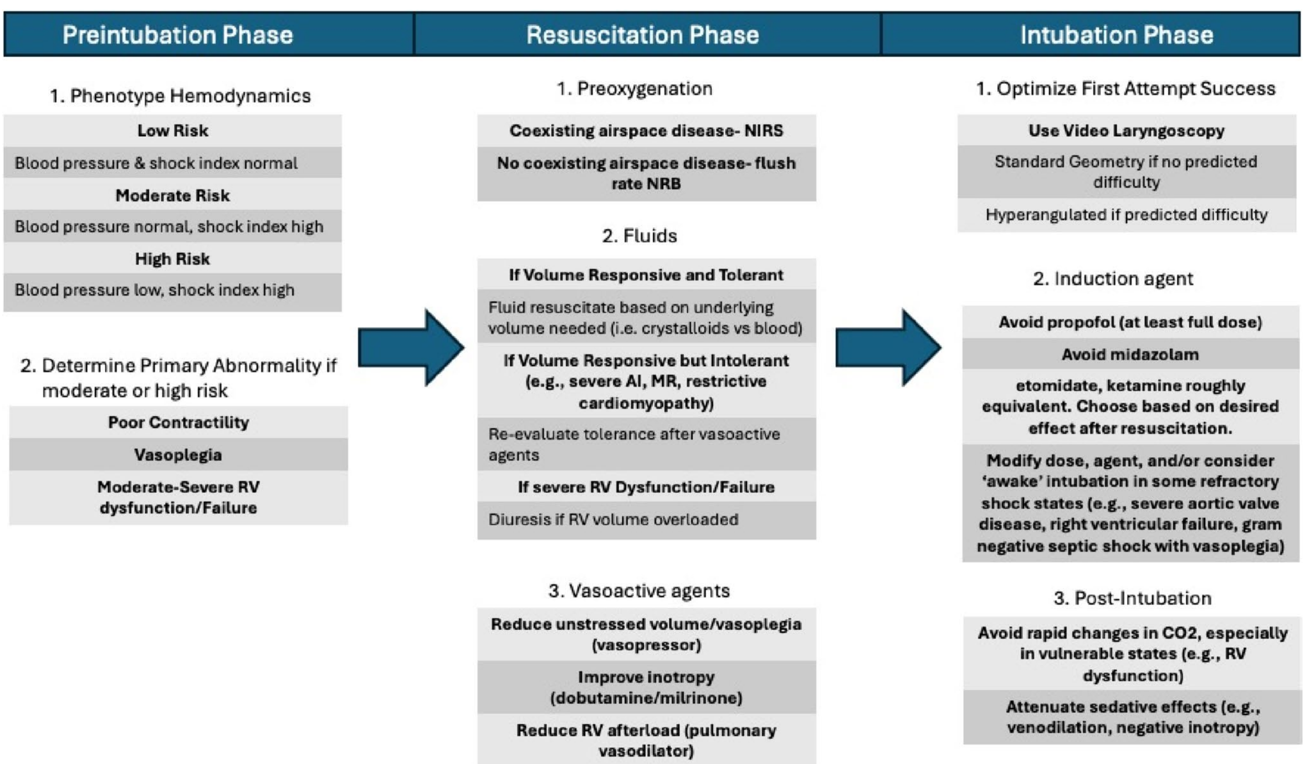

Fig. 2 Personalized resuscitation. Preintubation resuscitation also requires a nuanced approach based on the underlying physiologic abnormalities and the expected change in those abnormalities with induction, apnea, intubation, and mechanical ventilation. RV = right ventricular, AI = aortic insufficiency, MR = mitral regurgitation, NIRS = noninvasive respiratory support, NRB = nonrebreathing mask

agent in patients with overt hemodynamic instability is likely to be an unsuccessful strategy if broadly applied.
8. Prophylactic pressors stabilize the initial preintubation state only. This is a very different clinical scenario than stabilizing the *change* in physiology with intubation. Thus, the pharmacologic adjuncts for intubation must be chosen based on the underlying physiologic state and the expected change.
9. Interesting physiology evidence suggests that rapid peri-intubation CO_2 changes, and not necessarily the positive pressure itself, play a role in postintubation hypotension. Until more evidence is available, we should be mindful of the rate at which we change CO_2 after intubation in hemodynamically fragile patients.
10. Current clinical trial methodologies and analytic strategies have limited ability to evaluate the complex relationships related to the physiologically difficult airway.

Conclusion

The physiologically difficult airway remains a complex and significant threat to critically ill patients. While much work has been done over the last 5 years, innovative trials and more sophisticated analyses are needed to explore the complex relationships between variables that increase risk. In the meantime, we must eliminate easily modifiable risks where possible and move to a more personalized approach to preintubation optimization based on underlying physiology.

Author Contribution JMM reviewed the literature and wrote and reviewed the manuscript.

Data Availability No datasets were generated or analyzed during the current study.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest JMM has received travel support from Fisher & Paykel.

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- • Of importance
- •• Of major importance

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