When to intubate in acute hypoxaemic respiratory failure? Options and opportunities for evidence-informed decision making in the intensive care unit

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The optimal timing of intubation in acute hypoxaemic respiratory failure is uncertain and became a point of controversy during the COVID-19 pandemic. Invasive mechanical ventilation is a potentially life-saving intervention but carries substantial risks, including injury to the lungs and diaphragm, pneumonia, intensive care unit-acquired muscle weakness, and haemodynamic impairment. In deciding when to intubate, clinicians must balance premature exposure to the risks of ventilation with the potential harms of unassisted breathing, including disease progression and worsening multiorgan failure. Currently, the optimal timing of intubation is unclear. In this Personal View, we examine a range of parameters that could serve as triggers to initiate invasive mechanical ventilation. The utility of a parameter (eg, the ratio of arterial oxygen tension to fraction of inspired oxygen) to predict the likelihood of a patient undergoing intubation does not necessarily mean that basing the timing of intubation on that parameter will improve therapeutic outcomes. We examine options for clinical investigation to make progress on establishing the optimal timing of intubation.

Lancet Respir Med 2024

Published Online
May 24, 2024
https://doi.org/10.1016/S2213-2600(24)00118-8

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Introduction

Acute hypoxaemic respiratory failure (AHRF) is a pathophysiological state characterised by arterial hypoxaemia.[1] AHRF is a common cause of critical illness, accounting for 10–15% of patients admitted to the intensive care unit (ICU) and 20–25% of patients who receive mechanical ventilation.[2,3] Patients with AHRF frequently require supplemental oxygen and ventilatory support to maintain adequate oxygenation and ventilation. Clinicians managing AHRF begin with less invasive forms of respiratory support, including non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), and progress to more invasive forms of respiratory support on the basis of the patient's physiological state (figure 1). In cases where HFNC or NIV is unsuccessful and the patient's status is declining, or when deemed necessary, clinicians might transition patients from NIV to invasive ventilation by performing endotracheal intubation.[4] The optimal timing for this intervention and the criteria used to define the timing are important areas of uncertainty in the management of AHRF.

The clinical quandary: timing of intubation

The optimal timing of intubation depends on the balance of potential benefits and harms of invasive mechanical ventilation in comparison with non-invasive oxygen strategies in a given patient (figure 1). With careful titration of sedation and ventilator settings to control respiratory drive and effort, invasive mechanical ventilation can prevent complications resulting from excessive respiratory muscle effort. These complications potentially include patient-self-inflicted lung injury (P-SILI), in which vigorous respiratory effort causes excessive lung strain and elevated transpulmonary pressure,[4–8] and diaphragm myotrauma, in which excess muscular loading causes muscular inflammation and sarcomeric disruption.[6] Early initiation of invasive mechanical ventilation in patients with vigorous respiratory efforts might avert P-SILI and diaphragm myotrauma, prevent progression of respiratory failure, and facilitate recovery (figure 1).

However, invasive mechanical ventilation also carries serious risks, including lung injury, pneumonia, and diaphragm dysfunction induced by ventilation, as well as delirium and neurocognitive impairment (possibly because of exposure to sedation), ICU-acquired weakness from sedation and immobility,[4,9,10] laryngeal injury, and post-traumatic stress disorder.[11,12] Peri-intubation risks

Key messages

- The decision to intubate is a high-stakes clinical decision that carries several potential risks and benefits for patients with acute hypoxaemic respiratory failure
- The timing of intubation varies considerably between individual clinicians, institutions, and geographical regions, even for patients with similar characteristics
- Various potential triggers for intubation could be used, individually or in combination, to assist in the decision to intubate and determine the timing of intubation
- Intubation triggers could include respiratory pressures and physiological metrics, circulating biomarkers, and clinical scores
- Challenges to identifying and investigating useful triggers for intubation include ethical concerns, clinical equipoise, the feasibility and validity of trigger measurement, and the complexity of designing clinical trials to establish the effect of intubation guided by particular triggers on patient outcomes
- Establishing useful physiological triggers to guide decision making about intubation for patients with acute hypoxaemic respiratory failure will help to maximise benefits and minimise harms in the use of invasive mechanical ventilation

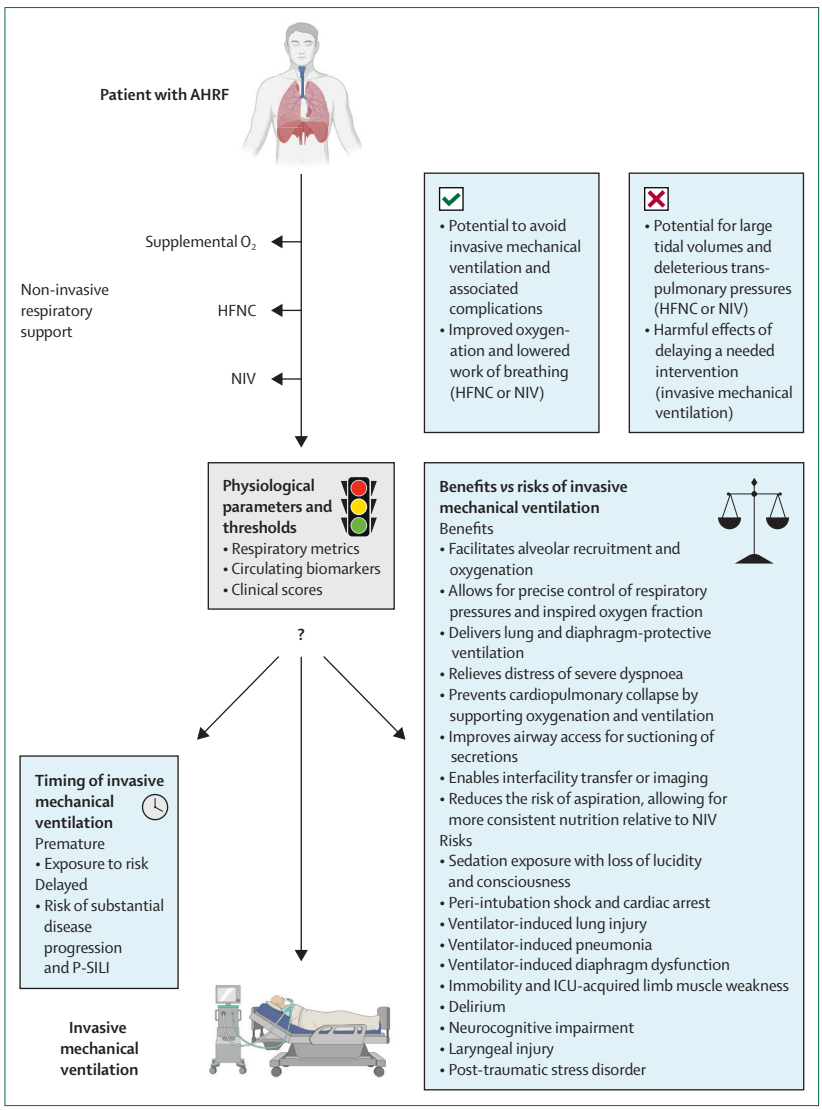

***Figure 1*: Possible progression of treatment and accompanying considerations for patients with AHRF**
Figure created with Biorender.com. Patients might benefit from a non-invasive method of respiratory support, depending on their physiological status. The risks and benefits of this must be carefully considered. If these methods are not supportive enough, a clinician could consider the escalation of breathing support to invasive mechanical ventilation. Again, the risks and benefits of this intervention, as well as the optimal timing of initiation (which is currently unclear) should be considered carefully. Physiological parameters and triggers have the potential to inform the decision and timing of intubation, facilitating a personalised approach to ventilatory support that will improve the outcomes of patients with AHRF. AHRF=acute hypoxaemic respiratory failure. HFNC=high-flow nasal cannula. ICU=intensive care unit. NIV=non-invasive ventilation. P-SILI=patient self-inflicted lung injury.

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include shock and cardiac arrest.[13] Compared with non-intubated patients, patients requiring invasive mechanical ventilation are at a higher risk of death, although the increased risk probably reflects important differences in the severity of illness.[14]

There are no established or widely accepted criteria to trigger intubation in patients with AHRF before cardiorespiratory arrest. Given the risks of invasive mechanical ventilation and the uncertain benefit associated with avoiding P-SILI and diaphragm myotrauma, many clinicians are hesitant to intubate patients and initiate invasive mechanical ventilation unless it is felt to be absolutely necessary to avert cardiopulmonary collapse (figure 1). Early intubation is supported by the rationale that preventing lung injury and diaphragm myotrauma by early intubation could avert catastrophic deterioration, mitigate disease progression, and promote more rapid recovery. Nonetheless, delaying intubation might avoid unnecessary exposure to the risks of invasive mechanical ventilation.

The balance of benefit and harm from intubation might vary over time as patients progress through the acute phase of illness. The exact timepoint at which the benefits of invasive mechanical ventilation outweigh its harms is likely to vary among patients according to both disease-specific characteristics (such as the cause of AHRF) and patient-specific characteristics (such as accessory muscle use). Crucially, there is no established systematic approach to weighing these various considerations to establish the optimal timing of intubation.

Limitations of the available evidence to guide the timing of intubation

Evidence to guide the decision about timing of intubation is limited by selection bias, difficulties defining time zero, and unmeasured confounding. Many studies that aim to compare the effects of early versus late intubation exclude patients who were never intubated.[15–19] However, this design is limited by the fact that the success of delaying intubation might lie in avoiding intubation altogether. Excluding patients who were never intubated spuriously increases the measured mortality rate in patients who did not receive early intubation. For example, in one study of patients with acute respiratory distress syndrome (ARDS), early intubation was defined as intubation on ICU day 2 and late intubation as intubation on ICU days 3–5.[20] Mortality at 60 days was 36% in the early intubation group, 56% in patients categorised under late intubation, and 26% in patients who were never intubated; the average mortality rate in the combined late or never intubated group was 36%, equivalent to the mortality in the early intubation group.[20] It is unclear how mortality would have changed had patients in the late or never group been intubated on ICU day 2.

Another methodological challenge is defining early versus late intubation. Defining intubation timing with reference to the time of admission to ICU or hospital has considerable limitations because of interindividual differences in disease progression and timing of hospital presentation. The timing of admission to ICU might vary between hospitals and even within the same hospital. Alternatively, the timing of intubation can be defined using physiological or clinical triggers in a time-dependent or time-independent manner.[21,22] A physiological time zero could serve as a reference point from which the relative timing of intubation could be defined.

Alternately, time-independent definitions of early versus later intubation could use higher or lower values of physiological severity, respectively, eliminating the temporal component that might differ for several reasons (figure 2).

Making the decision to intubate is a complex, multifactorial process for which there is no standardisation or evidence-based consensus. Without stronger evidence to guide decision making, practice might vary according to non-physiological characteristics such as patient ethnicity or gender.[23] Well designed clinical trials are needed to inform practice. Ideally, these trials should test a range of different triggers for intubation on the basis of different clinical, biological, or physiological thresholds that account for a patient's illness trajectory. Here we briefly survey a range of parameters (details of the search strategy are in the appendix) that might be used to guide the decision to intubate.

Potential triggers for intubation

We have classified potential triggers for intubation into three categories: respiratory pressures and metrics, biomarkers, and clinical scores. These parameters, including proposed values to trigger intubation and the current feasibility of application, are described in the table. The ideal parameter and accompanying trigger for intubation might also vary for different respiratory support modalities.

Respiratory metrics

Respiratory metrics reflecting pulmonary mechanics and gas exchange serve as logical measures to assess patients in respiratory failure and evaluate the potential benefit of initiating invasive mechanical ventilation. Most patients with AHRF who receive invasive ventilation do so for respiratory reasons.[47,48] However, respiratory parameters might not capture additional nuances that clinicians incorporate into their decision making, such as haemodynamics, neurological status, or airway patency.[49]

Rapid shallow breathing index

The rapid shallow breathing index (RSBI) is a simple ratio calculated as the respiratory rate divided by the tidal volume and can be measured during face mask NIV.[24] This ratio provides insight into the breathing pattern of a patient and can help to identify patterns that are indicative of respiratory distress, usually an elevated respiratory rate and lower tidal volume. The RSBI is commonly used as an index to determine readiness for extubation but could be applied in reverse to determine need for intubation. Individuals undergoing NIV with RSBI values higher than 105 had a significantly elevated risk of intubation (odds ratio [OR] 3·70) compared with patients with RSBI values lower than this threshold.[24] In another study in AHRF, RSBI was substantially lower in patients successfully managed with NIV than in those who ultimately received intubation.[25] RSBI might be sensitive to the pressure support level applied on NIV, and further work would be needed to standardise the measurement conditions under which RSBI is measured.

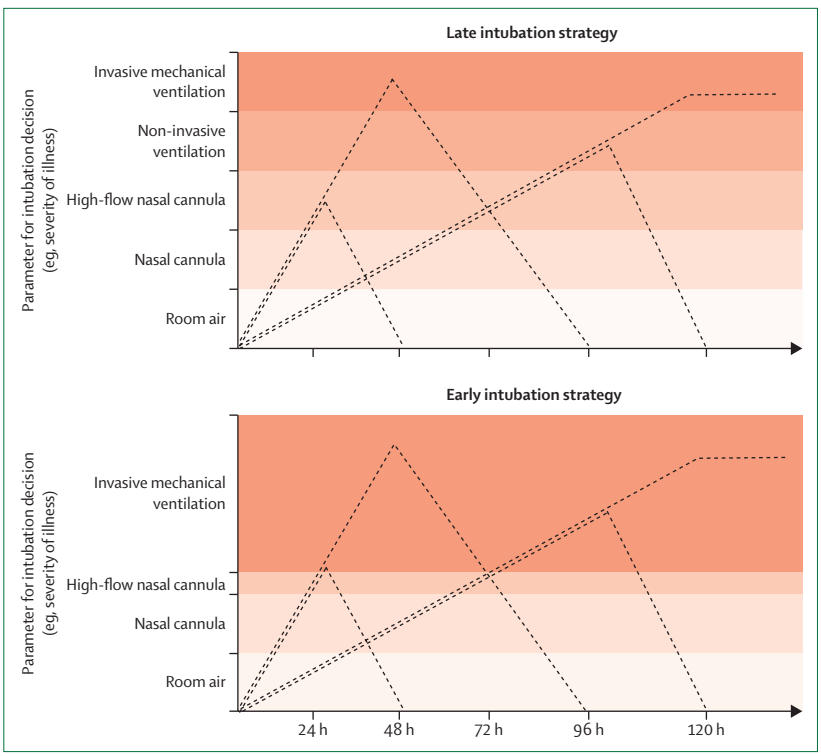

Figure 2: **Strategies for early versus later intubation based on higher or lower values of physiological severity**
Conceptual diagrams showing the potential progression of patients with AHRF through different phases of illness, with four possible patient trajectories plotted as dotted lines. The y-axes show the increasing severity of a particular parameter such as ROX index or PaO_2/FiO_2, and the x-axes show time. The colour of the rectangles in each panel shows the relationship between parameter severity and the respiratory support strategy. As parameter severity increases for a given patient, they progress from room air to nasal cannula to high flow nasal cannula. Some patients progress to invasive ventilation, but the parameter value that triggers invasive ventilation differs between the late intubation strategy (upper panel) and early intubation strategy (lower panel). Initially, all patients have increasing severity (dotted lines with upward slope). Each patient reaches their maximum severity (highest point of each dotted line) at different times. From this peak, three patients improve (dotted lines with downward slope), although one maintains the same severity (dotted line with horizontal slope). These trajectories show how adjusting the trigger value for a particular parameter can define an early or late intubation strategy. PaO_2/FiO_2=ratio of arterial oxygen tension to fraction of inspired oxygen.

See **Online** for appendix

PaO_2/FiO_2 ratio

The ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) is used to diagnose AHRF and grade its severity.[26] A large multicentre study of patients with ARDS (LUNG SAFE) found that the PaO_2/FiO_2 ratio was associated with NIV outcome and that success rates of NIV decreased as the severity of hypoxaemia worsened.[14] The risk of ICU mortality was higher in patients with moderate or severe ARDS (PaO_2/FiO_2 <150 mm Hg) who were initially managed with NIV than in those who received invasive mechanical ventilation within 1–2 days of fulfilling ARDS criteria.[14] The appropriateness of using NIV and the need for intubation might, therefore, depend on the severity of hypoxaemia. Delbove and colleagues found that among patients with ARDS undergoing

	Rationale	Proposed component of trigger for intubation	Readiness for clinical trials
Respiratory parameters			
Rapid shallow breathing index	Measures abnormal breathing pattern indicative of respiratory distress	>105 breaths per min[24,25]	Ready
PaO_2/FiO_2	The primary metric used to determine AHRF severity	<150 mm Hg[14,26–29]	Ready
ROX index	A simple score that evaluates respiratory rate and oxygenation status	<2·7–4·88 (cutoff values vary between studies)[30–34]	Ready
VOX index	A simple score that evaluates tidal volume and oxygenation status	>20·91 at 2 h or >22·67 at 6 h[35]	Ready
Airway oscillometry parameters	A technique that yields various respiratory parameters that could be relevant to the decision to intubate	No specific value identified currently	Needs further evaluation to establish feasibility and performance
Dyspnoea score	A scaled score of patient-reported dyspnoea	>4 after an initial NIV session[36,37]	Ready
ΔP_{es}	A surrogate measure of pleural pressure and inspiratory effort	Decrease in ΔP_{es} <10 cm H_2O after initiating NIV[7,38]	Needs further evaluation to establish feasibility and performance in non-intubated patients
ΔP_{nose}	A minimally invasive measure of inspiratory effort	Uncertain	Needs further evaluation to establish feasibility and performance
$P_{0.1}$	A measure of the force generated against a brief end-expiratory occlusion indicating respiratory drive	Uncertain	Needs further evaluation to establish feasibility and performance
P_{occ}	A measure of force generated against an end-expiratory occlusion, indicating inspiratory effort	Uncertain	Needs further evaluation to establish feasibility and performance
Diaphragm thickening fraction	A measure of diaphragm contractility	Uncertain	Needs further evaluation to establish specific trigger values
Circulating biomarkers			
Serum CRP	A systemic inflammatory marker (only studied in COVID-19)	>32·5 mg/L upon presentation or >97 mg/L at maximal levels[39]	Ready
Ferritin	An inflammatory marker upregulated by inflammatory cytokines	>456·2 ng/mL[40]	Ready
D-dimer	A general measure of coagulation activation (only studied in COVID-19)	No specific value identified currently	Needs further evaluation to establish specific trigger values
IL-6	A pro-inflammatory cytokine	>35 pg/mL upon presentation or >80 pg/mL at maximal levels[39]	Would benefit from further evaluation in non-COVID-19 populations
Lymphocyte count	A measure of adaptive immune activation	<0.7 cells per μL[40]	Would benefit from further evaluation in non-COVID-19 populations
Neutrophil-to-lymphocyte ratio	A measure of inflammatory status	>4.94[41]	Would benefit from further evaluation in non-COVID-19 populations
Lactate dehydrogenase	A non-specific measure of tissue damage	No specific value identified currently	Needs further evaluation to establish specific trigger values
Integrative clinical Scores			
APACHE II score	A comprehensive scoring system with several respiratory-specific factors	≥10[42]	Ready
HACOR score	A multivariable score including several important respiratory parameters	>5 or no decrease during therapy[43–45]	Ready
Updated HACOR score	A multivariable score that adds several clinical characteristics and values to the HACOR score	>14[46]	Ready
Intubation criteria used in randomised trials	Multisystem criteria encompassing various triggers for intubation	The literature indicates discordance between numbers of patients meeting criteria and numbers intubated[47,29]	Needs further evaluation to determine how to integrate various previously used criteria

The trigger values for each row correspond to potentially relevant physiological thresholds that could, perhaps in combination with other information or proposed components of triggers, comprise a useful set of criteria making up a trigger for intubation. Biomarkers are to be used in combination with other parameters and could be tailored to the underlying cause of acute hypoxaemic respiratory failure and associated pathophysiology. APACHE II=Acute Physiology and Chronic Health Evaluation II. CRP=C-reactive protein. HACOR=Heart rate, acidosis, consciousness, oxygenation, and respiratory rate. IL-6=interleukin-6. PaO_2/FiO_2=ratio of arterial oxygen tension to fraction of inspired oxygen. ΔP_{es}=change in oesophageal pressure. ΔP_{nose}=change in nasal pressure. $P_{0.1}$=airway occlusion pressure. P_{occ}=expiratory occlusion pressure. ROX=respiratory rate and oxygenation. VOX=tidal volume and oxygenation.

Table: **Physiological parameters and triggers to aid in the decision to intubate**

HFNC, lower PaO_2/FiO_2 was associated with a higher risk of intubation.[27] Multiple additional studies suggest that low PaO_2/FiO_2 ratios (<150 mm Hg or <200 mm Hg) on NIV are associated with eventual intubation.[26,28,29] There are several important considerations for this measure, including the requirement for an arterial line or puncture to measure arterial blood gas concentrations, the potential inaccuracy of FiO_2 assessment during NIV or HFNC due to entrainment of room air and leakage, and the systematic effect of FiO_2 on the PaO_2/FiO_2 ratio.[50] As PaO_2/FiO_2 only captures oxygenation and does not reflect the minute ventilation or respiratory effort required to attain that degree of oxygenation, others have proposed modifications using the $PaCO_2$ or respiratory rate.[30,51,52]

ROX index

The ROX index was initially proposed in 2016 as a prognostic score for patients with AHRF due to pneumonia. ROX is computed as the ratio of peripheral oxygen saturation to fraction of inspired oxygen divided by the respiratory rate ($[SpO_2/FiO_2]$/respiratory rate).[30] Roca and colleagues defined a cutoff of 4·88 after 12 h of HFNC therapy; values exceeding this threshold were associated with a lower risk of intubation (OR 0·27).[30] The validity of the ROX index to predict need for intubation after HFNC therapy was subsequently externally validated in multiple cohorts of patients with AHRF;[31] ROX index values less than 3·85 after 12 h of HFNC therapy were associated with HFNC failure, with sensitivity of 23·5% and specificity of 98·4%.[31] No improvement in the ROX index between 2 h and 12 h after initiation of HFNC initiation also indicated a higher risk of intubation. In patients with COVID-19-induced AHRF, researchers identified an optimal ROX index threshold of 5·99 to predict intubation, suggesting that different triggers might be warranted according to the cause of AHRF and unique disease characteristics.[32] A meta-analysis published in 2021 found that the ROX index had reasonably strong discriminatory value in predicting the receipt of NIV or intubation among patients on HFNC (summary area under the curve=0·81).[33] One caveat is that an increase in HFNC flow might result in corresponding changes in the ROX index at the same fraction of inspired oxygen.[53] The ROX index has also been used in randomised controlled trials of non-invasive respiratory support as a threshold for intubation. For example, Al Hashim and colleagues used a ROX index of less than 2·85 after 2 h of HFNC therapy or less than 3·85 after 12 h of therapy to define failure of HFNC and trigger intubation.[54]

VOX index

The VOX index is a proposed modification of the ROX index.[35] It is calculated as (SpO_2/FiO_2)/tidal volume measured during a facemask NIV trial[35] on the basis that tidal volume is a better reflection of the early increase in respiratory drive than respiratory rate, which only increases once the respiratory drive has increased 3–4-fold. This concept is supported by the observation that patients with NIV failure have increased tidal volume but not increased respiratory rate.[7] In one small study, the VOX index was a better predictor of invasive mechanical ventilation initiation among patients on HFNC, compared with the ROX index.[35]

Forced oscillometry to assess respiratory mechanics

Forced oscillometry involves the application of sinusoidal pressure waves to airspaces through the emission of sounds at different frequencies to estimate pressure–volume relationships in different lung compartments.[55,56] Several important respiratory mechanics parameters can be assessed in non-intubated patients using forced oscillometry, including airway resistance and reactance.[55,56] The area under the reactance curve also provides valuable insights regarding the overall elasticity of the lung and the closure of small airways.[56] Assessing the elastic properties of the lung via forced oscillometry could help to detect patients at risk of P-SILI during NIV or HFNC and might provide a relevant measure of the response of the patient to non-invasive therapies.[55,57] However, this technique is limited by the need to transiently remove oxygen or breathing support from the patients during measurement (ie, for 20–30 s), which might cause hypoxaemia in some patients who are highly dependent on NIV or HFNC.

Patient-reported dyspnoea

Dyspnoea can be quantified using a visual analogue scale or Borg scale. Dyspnoea measures predict ICU mortality, 90-day mortality, length of hospital stay, risk of intubation within 28 days, and ventilator-free days.[36] In a prospective observational study, Dangers and colleagues used a modified Borg scale to assess dyspnoea in patients with acute respiratory failure undergoing NIV and classified them according to a threshold of 4 points (out of 10) on the scale before and after a session of NIV.[36] Individuals with dyspnoea scores of 4 or more had a higher risk of NIV failure than those with scores less than 4 (defined as intubation or death; OR 2·4, 95% CI 1·5–3·9).[36] In a separate study, patients with moderate-to-severe dyspnoea measured on a visual analogue scale had fewer days free of respiratory support (ie, NIV or invasive mechanical ventilation) and fewer days free of invasive ventilation at both 28 and 60 days.[37] Compared with those with mild or no dyspnoea, patients with moderate-to-severe dyspnoea at ICU admission had significantly higher rates of intubation (OR 3·8, 95% CI 1·5–9·9), even after adjusting for severity of disease and degree of hypoxaemia.[37] Patient-reported dyspnoea assessments are simple in non-intubated patients and can aid in clinical decision making regarding a patient's respiratory support. However, pain, sedation, language barriers, and delirium or altered mental status might interfere with dyspnoea assessment in some patients,

and differences in subjective reporting of dyspnoea across individuals and populations could, in theory, obscure the relationship between particular dyspnoea triggers and the benefit of invasive ventilation.

Assessment of accessory respiratory muscle use

The use of accessory respiratory muscles, including the sternocleidomastoids, intercostals, and abdominals, can indicate potentially unsustainable work of breathing.[58,59] Studies using electromyography suggest a reliable sequence of accessory muscle activation in the response to progressive respiratory failure.[60–63] As respiratory load progressively increases, the diaphragm and intercostal muscles first increase activity, then the sternocleidomastoids are activated, and, finally, the abdominal muscles begin to contract to augment expiratory flow and enhance the inspiratory muscle length-tension relationship. Accessory muscle use also correlates with dyspnoea.[64] Recruitment of accessory muscles, measured by inspection, palpation, ultrasound, or surface electromyography, could be incorporated into triggers for intubation.[65,66] However, accessory muscle recruitment does not always indicate an unsustainable work of breathing, as in the case of some patients with chronic obstructive pulmonary disease.[67] Most research assessing accessory muscle activation was done in healthy volunteers or patients weaning from mechanical ventilation. An additional limitation is that measurement by inspection or palpation could be unreliable, and measurement by surface electromyography in deteriorating patients remains impractical.

Ultrasound of the diaphragm and other respiratory muscles

Point-of-care ultrasound provides a means of quantifying respiratory muscle contraction that could be incorporated into intubation triggers.[68] Respiratory muscles that can be assessed by ultrasound include the diaphragm, sternocleidomastoid, parasternal intercostals, and abdominals. The contractility of diaphragm muscles is measured by ultrasound, using the diaphragm thickening fraction (Tfdi). Tfdi reflects both tidal effort and muscle weakness.[69] Mercurio and colleagues found that the Tfdi could predict NIV outcome in patients with AHRF with an optimal threshold value (ie, 36–37%); patients with lower values were more likely to fail NIV.[70] Dargent and colleagues did not find that Tfdi was significantly associated with success or failure of NIV but did find that on repeat assessment, patients who were intubated had increases in Tfdi over time.[71] Clinicians require training to be able to produce accurate and reproducible Tfdi measurements, especially when patients have high respiratory rates.

Ultrasound of the accessory muscles of respiration can complement diaphragmatic ultrasound. Thickening of the parasternal intercostal muscles inversely correlates with respiratory support in patients receiving mechanical ventilation.[72,73] Abdominal muscle contraction with expiration can also be visualised and quantified sonographically.[74] The sternocleidomastoid is another potential target for bedside ultrasound. For ultrasound of the accessory muscles of respiration, specific thresholds that could inform intubation decisions have yet to be established.

Measures of inspiratory effort: ΔP_{es}

Oesophageal pressure provides a surrogate measure of pleural pressure.[75,76] The change in oesophageal pressure (ΔP_{es}) reflects the pleural pressure swing during inspiration and is often used as a measure of inspiratory effort[38] to gauge the risk of P-SILI and diaphragm myotrauma. The response in ΔP_{es} to the application of NIV predicts NIV failure.[7] Specifically, a decrease in ΔP_{es} of at least 10 cm H_2O after 2 h of NIV was associated with a markedly lower probability of intubation.[7] This finding suggests that failure to alleviate excess respiratory effort following the application of NIV might be a reliable identifier of future need for intubation. Grieco and colleagues also found that a decrease in ΔP_{es} following the application of helmet NIV was associated with a lower risk of intubation.[77] However, some non-intubated patients might not tolerate the insertion of an oesophageal balloon catheter for monitoring of ΔP_{es}, and oesophageal manometry might not capture the recruitment of abdominal muscles as accessory muscles of respiration.[75,76]

Surrogate measures of inspiratory effort: P_{nose}

Another promising surrogate for inspiratory effort in non-intubated patients is the nasal pressure swing generated during tidal breathing (ΔP_{nose}). Tonelli and colleagues showed that ΔP_{nose} is highly correlated with ΔP_{es}[78] and accurately predicts HFNC failure, with similar performance to the ROX index.[79] This pressure can be measured in a less invasive manner than oesophageal manometry and provides similar information.

Surrogate measures of inspiratory effort: $P_{0\cdot1}$

The airway occlusion pressure generated in 100 milliseconds ($P_{0\cdot1}$) is used to quantify respiratory drive and has been shown to predict respiratory effort in mechanically ventilated patients.[80,81] In theory, $P_{0\cdot1}$ should reflect elevated respiratory effort and risk of P-SILI.[81–84] One study found that $P_{0\cdot1}$ could feasibly be measured in patients undergoing NIV but did not predict the risk of subsequent intubation.[71]

Surrogate measures of inspiratory effort: P_{occ}

The expiratory occlusion pressure (P_{occ}) is measured as the change in airway pressure during an inspiratory effort against an occluded airway.[85] P_{occ} directly reflects inspiratory effort and allows the calculation of the total dynamic lung stress across the inspiratory phase, as validated by multiple studies.[85,86] To date, no study has reported measuring P_{occ} during NIV, and its utility as a predictor of need for intubation remains to be assessed.[68–70]

Circulating biomarkers

Biomarkers arise from underlying physiological and cellular processes and might usefully inform the decision to intubate. Circulating biomarkers might, in combination with other clinical information such as the degree of hypoxaemia, work of breathing, and level of consciousness, help to guide clinicians in the application of respiratory support, including invasive ventilation.[87,88] Here, we focus on inflammatory markers, leukocyte counts, and lactate dehydrogenase, although other circulating biomarkers have been investigated in the context of respiratory failure.[89]

Inflammatory markers

Pulmonary and systemic mediators of inflammation play a fundamental role in the pathogenesis of lung injury and multiorgan failure. Inflammatory markers, therefore, represent a broad category of factors that could help in the assessment of the risk of P-SILI, diaphragm myotrauma, and progression of illness. Among patients with COVID-19-induced AHRF who were treated with NIV or HFNC, the concentration of C-reactive protein (CRP) was significantly higher in patients who eventually received intubation than in those who did not.[28,90] Serum ferritin was also associated with the risk of intubation in patients undergoing NIV.[40] Higher D-dimer concentrations were associated with a higher risk of intubation and death in patients with COVID-19-induced AHRF.[91] Another study found no significant differences between serum ferritin or D-dimer concentrations on the basis of NIV outcome among patients with COVID-19-induced AHRF, although values were missing for over half of the patients.[92] Maximal values of IL-6 and CRP were highly predictive of intubation risk in patients with COVID-19-induced AHRF (area under the curve [AUC] >0·8).[39] Biomarkers could help to identify biological subphenotypes of patients with AHRF treated with non-invasive support who might differ in their relative benefit or harm from invasive ventilation. The value of inflammatory markers to predict intubation in AHRF is substantially increased by adding additional variables to improve accuracy and specificity.

Leukocyte counts

Zablockis and colleagues reported that a lymphocyte count below a threshold of 0·7 cells per mm³ was predictive of NIV failure and intubation in patients with COVID-19-induced AHRF (AUC=0·7)[40] The neutrophil-to-lymphocyte ratio may provide a measure of ARDS pathogenesis by reflecting the presence of excessive numbers of neutrophils and decreased numbers of lymphocytes. Tatum and colleagues observed that a neutrophil-to-lymphocyte ratio equal to or greater than 4·94 predicted intubation in patients hospitalised for COVID-19-induced AHRF.[41] Farhadi and colleagues also found that in patients with COVID-19-induced AHRF, the neutrophil-to-lymphocyte was higher in those who received intubation than in those who did not.[93] Of note, this association might be particular to COVID-19-induced AHRF, given its specific viral pathogenesis.

Lactate dehydrogenase

Lactate dehydrogenase is a non-specific indicator of tissue damage. Multiple studies have shown that lactate dehydrogenase, measured on admission or initiation of HFNC or NIV initiation, can aid in the prediction of NIV or HFNC outcomes for patients with AHRF.[90,92,94] In several studies of patients with AHRF, lactate dehydrogenase was higher in patients who ultimately required intubation after NIV or HFNC than in patients who were sustained on NIV or HFNC without intubation.[90,92,94] Menga and colleagues found that in patients with COVID-19-induced AHRF, lactate dehydrogenase on admission was independently associated with NIV failure and intubation.[90] A lactate dehydrogenase threshold of 405 and a clinical score (Simplified Acute Physiology Score II) threshold of 32 predicted intubation with sensitivity of 43% and specificity of 91%.[90]

Although biomarkers might not be relevant triggers for intubation when considered in isolation, they might help in identifying patients with pulmonary or systemic inflammation who are at an increased risk of developing P-SILI or having a severe clinical course. Combining biomarkers with clinical parameters more directly reflective of respiratory status might provide a more complete and accurate depiction of the benefit of invasive mechanical ventilation for a particular patient.

Integrative clinical scores

Clinical scores integrate some of the factors described in the previous two sections and, thus, could increase accuracy and predictive value by combining salient parameters.

APACHE II

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is a widely used prognostic score in critical illness and includes several respiratory-specific criteria.[95] Higher APACHE II scores are associated with failure of non-invasive respiratory support and eventual intubation in patients with AHRF in multiple studies[35,42,43,94] although not in all.[31,79] Scores intended to capture multiorgan dysfunction, such as the APACHE II score, are most compelling as triggers for intubation when organ dysfunction is plausibly a consequence of respiratory failure.

HACOR score

A scale that considers heart rate, acidosis, consciousness, oxygenation, and respiratory rate (termed the HACOR score) has been used to predict failure of NIV in patients with AHRF.[44] The initial validation study found that this score had 76% sensitivity and 93% specificity for

***Panel 1*: Intubation criteria used in selected clinical trials related to noninvasive respiratory strategies in acute hypoxaemic respiratory failure**

Antonelli et al (2001)[97]
Any of the following criteria can be used:

Respiratory
- Failure to maintain arterial oxygen tension (PaO_2) >65 mm Hg with a fraction of inspired oxygen (FiO_2) ≥0·6
- Excessive tracheal secretions
- Inability to correct dyspnoea
- Inability of the patient to tolerate a face mask

Neurological
- Development of conditions necessitating endotracheal intubation to protect the airways—ie coma or seizure disorders

Cardiovascular
- Any haemodynamic or electrocardiographic instability, ie, systemic hypotension lasting more than 1 h despite fluid resuscitation

Ferrer et al (2003)[98]
Any of the following criteria can be used:

Respiratory or cardiovascular
- Respiratory or cardiac arrest
- Respiratory pauses or heart rate <50 bpm with loss of alertness or gasping for air
- Evidence of exhaustion, such as active contraction of the accessory muscles with thoracic-abdominal paradoxical movement; massive aspiration or inability to manage respiratory secretions properly
- Haemodynamic instability without response to fluids and vasoactive agents

Neurological
- Major agitation inadequately controlled by sedation

Honrubia et al (2005)[65]
Criteria are acute hypoxaemic or hypercapnic respiratory failure due to a preexisting cause plus three of:
- PaO_2/FiO_2 ratio ≤170
- Respiratory rate ≥35 breaths per min
- Blood pH ≤7·30
- Score of 3–5 on the Kelly scale of neurological dysfunction
- Score of ≥3 points on a modified scale of accessory respiratory muscle use (1=no visible respiratory activity in the neck muscles; 2=respiratory activity in the neck muscles without active contraction of supraclavicular or intercostal muscles; 3=vigorous activity of accessory muscles with contraction, and 4=vigorous activity with contraction of accessory muscles and paradoxical abdominal breathing pattern)

Frat et al (2015)[47]
Criteria are signs of persisting or worsening respiratory failure, defined by at least two of:
- Respiratory rate >40 cycles/min
- No improvement of signs of respiratory muscle fatigue
- Development of copious tracheal secretions
- Acidosis with a pH <7·35
- Saturation of peripheral oxygen (SpO_2) <90% for >5 min without technical dysfunction
- Intolerance to non-invasive ventilation (NIV)

Alternatively, one of the following criteria can be used:
- Haemodynamic instability (defined by systolic blood pressure <90 mm Hg, mean arterial blood pressure <65 mm Hg, or requirement for vasopressor)
- Deterioration of neurological status (Glasgow coma scale <12 points)

Azoulay et al (2018)[99]
Any of the following criteria can be used:

Respiratory or cardiovascular
- Severe haemodynamic instability requiring norepinephrine or epinephrine >0·3 µg/kg per min
- Cardiorespiratory arrest
- Ongoing myocardial infarction,
- Severe retention of airway secretions
- Worsening of respiratory distress (SpO_2 <92% or respiratory rate >40/min regardless of oxygen flow rate or use of accessory respiratory muscles)
- Inability to maintain PaO_2 >65 mmHg with FiO_2 >0·6
- Dependency on NIV with inability to remain off NIV for longer than 2 h
- >50% increase in the time on NIV from one day to the next

Neurological
- Severe encephalopathy (Glasgow coma scale <11)

Darreau et al (2020)[100]
Criteria are neurological failure (Glasgow coma scale <10) or two of the following criteria relating to respiratory failure:
- Oxygen saturation <90% for >5 min despite optimised oxygen administration
- Respiratory rate >35 per min
- Significant use of accessory respiratory muscles
- Respiratory acidosis defined by pH <7·35 and pCO_2 >45 mm Hg
- Hypoxaemia with PaO_2/FiO_2 ratio <150
- Inability to cough or clear tracheal secretions

(Continues on next page)

predicting NIV failure and intubation after 1 h of NIV in patients with AHRF.[44] Subsequent studies reported that among patients undergoing NIV or HFNC, those who received intubation had higher HACOR score than those who did not receive intubation, as early as after 1 h of treatment.[45,79,96] To improve its predictive value, the HACOR score was updated in 2022 to include several other baseline characteristics and another clinical score (SOFA).[46] In a prospective multicentre observational study, the updated HACOR score yielded an AUC of 0·78

(Panel 1 continues from previous page)

Carrié et al (2023)[101]

Any of the following criteria can be used:

- Cardiac arrest or significant haemodynamic instability
- Worsening of neurological status
- Acute respiratory failure defined by at least two of the following criteria:
  - Respiratory rate ≥35/min
  - High respiratory-muscle workload
  - Abundant tracheal secretions
  - Signs of respiratory exhaustion (pH <7·32 or $PaCO_2$ >50 mmHg) with or without severe hypoxaemia (PaO_2/FiO_2 ratio <100 or SpO_2 <92% for more than 5 min)
- A rescue NIV trial was allowed at the discretion of the physician in patients with acute respiratory failure and no other organ dysfunction; persistence of worsening of acute respiratory failure or severe hypoxaemia after 1 h of NIV or in patients with NIV intolerance were considered as criteria for endotracheal intubation
- NIV dependence (defined as the resumption of acute respiratory failure or severe hypoxaemia under conventional oxygen therapy or high-flow nasal cannula oxygen with need for continuous NIV ≥12 consecutive hours)

for the prediction of intubation in patients with AHRF undergoing NIV after 1–2 h of therapy, compared with an AUC of 0·71 using the original HACOR score.[46]

Intubation criteria used in previous randomised trials

Researchers have attempted to specify systematic criteria for intubation in an effort to standardise outcomes in clinical trials evaluating non-invasive respiratory support strategies in AHRF (panel 1).[22,34,47,65,99–102] These criteria include haemodynamic, neurological, and respiratory indications for invasive mechanical ventilation.[13]

Preliminary findings suggest that these criteria are sensitive but not specific, in that most patients who are intubated have satisfied the criteria before intubation but many patients who satisfy the criteria do not receive intubation. In a recent randomised trial of helmet NIV, independent expert chart review deemed that only one of 48 patients who were intubated did not meet the prespecified criteria for intubation.[102] Another recent trial reported that all 346 intubated patients included in the study met prespecified intubation criteria.[48] However, neither trial recorded the proportion of patients who met the criteria and were not intubated. In a prospective cohort of patients with septic shock, only 50% who met prespecified criteria were intubated within 8 h.[100] In a retrospective cohort of patients with AHRF, only 9–13% of those who met similar prespecified criteria were intubated within 3 h of meeting those criteria.[22] A systematic review of trials of non-invasive treatments for respiratory failure identified seven trials in which the rate of meeting prespecified criteria for intubation was reported alongside the actual rate of intubation and found that only 40% of patients who met prespecified criteria also received intubation.[103] These findings reflect that the criteria for intubation used in randomised controlled trials might not reflect real-world clinical practice.

Challenges to testing the hypothesis

We have surveyed a range of clinical, physiological, and biological parameters that might be used as triggers for intubation in a future clinical trial of early versus late intubation strategies. Several open questions remain about the timing of intubation in AHRF (panel 2), and some specific issues should be considered regarding trial design.

***Panel 2*: Open questions in the timing of intubation in acute hypoxaemic respiratory failure**

- What disease-characteristic, patient-characteristic, and treatment-specific characteristics dictate the optimal timing of intubation?
- What is the best way to determine the timing of intubation to account for interindividual differences in disease progression and timing of hospital presentation?
- What parameters and what threshold values of those parameters to trigger intubation should be studied in randomised controlled trials?
- How can randomised controlled trials of various intubation timing strategies be designed to overcome strongly held opinions among clinicians around the appropriate timing of intubation and collect the variables needed to identify patients who might benefit from early intubation in the setting of a time-sensitive medical procedure?

First, the ethics of assigning patients randomly in a medical experiment is predicated on clinical equipoise. Establishing the boundaries of clinical equipoise by defining the population of patients with AHRF for whom there is genuine uncertainty about the timing of intubation is crucial to ensuring that the a clinical trial of early versus late intubation is ethical. Whether these boundaries should be specified in the trial design or by the treating clinician is uncertain; the STARRT-AKI trial provides an exemplar of one approach to establishing equipoise in a trial of timing of intervention.[34]

Second, the relevance of many of the parameters that we have discussed is predicated on their association with intubation. However, showing that eventual intubation is probable is not the same as showing that immediate intubation is beneficial. Our view is that

predictive scores that estimate the benefit of invasive ventilation can only be reliably formed using data from randomised trials. In the interim, prognostic scores could be used to select a population at high risk for requiring invasive mechanical ventilation, in whom a trial of earlier versus later intubation would be of great interest and relevance.

Third, the feasibility and measurement validity of relevant parameters need to be established. Although some respiratory parameters have appealing face validity because of their connection to P-SILI or respiratory decompensation, the required measurement techniques (eg, measurement of oesophageal pressure swing and oscillometry) need to be evaluated to confirm their feasibility and reproducibility in non-intubated patients with AHRF. One possible study design is a multicentre, prospective, observational study involving patients with AHRF, in which clinicians use their judgement to guide ventilatory support and intubation decisions, and important physiological parameters (to be tested in the subsequent phase) are measured, documented, and compared with whether and when patients are intubated.

Fourth, when designing a trial of early versus late intubation, we must not only identify which parameter to use to guide the intubation decision but also establish the optimal threshold value for that parameter to trigger early or late intubation. It might also be beneficial to consider the trajectory of the particular trigger such that it must be met for a specific duration of time or is assessed serially to assess trends over time.

Fifth, multiple factors could interact to modify the optimal timing of intubation. The extent to which P-SILI is relevant for non-intubated patients remains uncertain. Even in scenarios where P-SILI is relevant and caused by respiratory effort, the injury resulting from excess lung stress and strain might be moderated by the severity of pulmonary and systemic inflammation. In this scenario, intubating a patient on the basis of measures of respiratory effort to prevent P-SILI would only be sensible in patients with higher degrees of pulmonary or systemic inflammation. Thus, the optimal trigger or threshold for intubation might depend on other relevant patient characteristics, such as the cause of the AHRF. It seems unlikely that there can be a one-size-fits-all approach to establish the optimal timing of intubation. Trial designs need to consider the heterogeneity of treatment effects and the potential for interactions between relevant parameters when the benefit of intubation and invasive ventilation is being assessed. These complexities might be addressed by innovative trial designs specifying multiple arms, each using a different parameter, and randomly assigning patients to groups on the basis of different thresholds of the trigger for intubation. Response-adaptive randomisation could concentrate patients in study arms that show the greatest promise. Random assignment of patients could be further stratified by characteristics that potentially modify treatment effect. Extensive work would be required to evaluate how such a trial would be powered (partly in order to establish the funding requirements) and to define the adaptive design rules to ensure appropriate operating characteristics. Embedding the trial within a platform trial environment using a pragmatic trial design philosophy could facilitate enrolment.

Such a trial will face many additional challenges, including the selection of an optimal outcome (mortality, ICU-free days, or functional outcomes), assent from clinicians to have patients participate, and timely consent from patients or their substitute decision makers. However, the effort required to design and conduct such a trial is worthwhile because without such efforts, millions of patients will continue to be exposed to non-evidence-based variation in the timing of intubation in clinical care instead of receiving invasive mechanical ventilation only when the benefits are proven to outweigh the risks.

Search strategy and selection criteria

We collected references for this Personal View from searches of Medline, Embase, Cochrane, and Web Of Science. Search parameters included articles published between Jan 1, 1950, to March 3, 2024. Three searchable chunks were used to answer the research question, namely acute hypoxaemic respiratory failure or acute respiratory distress syndrome (and synonyms), AND endotracheal intubation (and synonyms), AND other keywords related to respiratory physiology and breathing support, for example, "ventilator weaning", "non-invasive ventilation", "work of breathing", "respiratory effort", "muscle fatigue", "diaphragm injury", and "predictor" and synonyms. More details on the specific search terms used for each database are in the appendix. Studies were limited to those involving patients aged 18 years and older. Only abstracts written in or translated into English were screened. When search results identified a particular parameter without multiple references on the topic, Google was used to explore the particular parameter to facilitate a comprehensive and accurate discussion of the topic.

Conclusions

Multiple physiological parameters, circulating biomarkers, and integrative clinical scores have shown prognostic value for the identification of patients who will undergo intubation. Such parameters have the theoretical potential utility to predict which patients would benefit from earlier versus later intubation. The establishment of validated clinical triggers to guide this process will greatly improve the application of invasive mechanical ventilation to promote the benefits, minimise the harms, and optimise the outcomes of this intervention for patients with AHRF.

Contributors

KGL, ECG, and CJY were involved in conceptualisation, tables and figures, literature appraisal, data interpretation, writing, and critical review. KGL did the literature search. JDC and MWS were involved in

data interpretation, tables and figures, writing, and critical review. OR and GR-S were involved in data interpretation, tables, writing, and critical review. All coauthors had responsibility for the decision to submit for publication.

Declaration of interests

No funding was received for the writing of this Personal View. KGL received a grant from the University of Toronto MHSc Medical Physiology programme to support any publication costs associated with this work. CJY reports funding from the Canadian Institutes of Health Research (Vanier Scholarship) and the Eliot Phillipson Clinician Scientist Program from the Temerty Faculty of Medicine at the University of Toronto. MWS was supported, in part, by grants from the US National Institutes of Health (NIH; National Center for Advancing Translational Sciences grant 5UL1TR002243 and National Heart, Lung, and Blood Institute grant K23HL143053) and by a grant from the US Department of Defense. MWS reports compensation from Baxter Healthcare for having served on a medical advisory board and for having delivered a virtual lecture at a conference. OR reports grants paid to his institution from Hamilton Medical and Fisher & Paykel Healthcare, as well as payment or honoraria for presentations from Hamilton Medical, Fisher & Paykel Healthcare, and Aerogen. OR participates on the data safety monitoring board for the CONFIDENCE trial and the OVERCOOL study. Outside the focus of the submitted work, OR has stocks or stock options in Tesai Care, a spin-off of Parc Taulí University Hospital, which focuses on respiratory muscle electrostimulation to improve weaning from invasive mechanical ventilation. ECG reports grants paid to his institution from the Canadian Institutes of Health Research and the National Sanitarium Association; consulting fees paid to him by Stimit, BioAge, LungPacer, and Zoll; payment or honoraria for presentations from Drager, Getinge, Vyaire, Lungpacer, Stimit; participation on an advisory board for Lungpacer and Getinge; leadership role as the chair of the PRACTICAL platform trial; and receipt of equipment for research from Timpel and Lungpacer. JDC has grants from NIH and the Department of Defense and a travel grant from Fisher & Paykel Healthcare to attend a scientific meeting and participates on the data safety and monitoring board for an NIH-funded trial. GR-S declares no competing interests.

Acknowledgments

The authors would like to thank the Department of Physiology at the University of Toronto for their financial support of the publication costs for this manuscript through the MHSc in Medical Physiology Mentored Literature Review Award.

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