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The "respiratory envelope", an aviation-inspired framework for patient tailored mechanical ventilation

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Abstract
Contemporary mechanical ventilation strategies in ARDS rely on lung-protective ventilation approaches that typically utilize separate static variables/settings (e.g., tidal volumes, plateau pressure) and cut-off values. This approach fails to capture complex patient dynamics. Increasing efforts have focused on the interactions between different parameters (e.g. mechanical power, driving pressure); however, these only accommodate a limited number of interactions and do not integrate the complexity of patient-specific, severity-dependent and time-varying thresholds for "safe" mechanical ventilation. In aviation, the "flight envelope" concept revolutionized flight safety by defining flexible, context-dependent boundaries as a function of multiple dimensions (e.g. flight speed, altitude, (dynamic) loads on the aircraft) within which an aircraft can operate. When a new aircraft is developed, its operational safety envelope is determined analytically. Calculations are quickly followed by flight simulations and flight testing, beginning from a known safe point within the envelope and gradually carefully exploring its boundaries to characterize its limits. Inspired by this aviation approach, we propose the "respiratory envelope" framework for mechanical ventilation: a conceptual framework that allows for the incorporation of multiple (time-dependent) dimensions and integrates interactions between ventilator variables/settings and patient characteristics. Just as flight envelopes informed the development of automated envelope protection algorithms and autopilot systems, a similar framework could be applied in clinical settings to simulate real-time "safety zones" based on continuously monitored, yet underutilized, physiological data, such as in digital twins.

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Introduction

Lung-protective mechanical ventilation strategies, utilizing uniform low tidal volumes, plateau and driving pressures (Fig. 1A) have markedly improved outcomes in patients with lung injury [1, 2]. Evolving insights have however shown that the risk of ventilator-induced lung injury may depend on lung compliance, recruitability, and interactions between ventilatory parameters (e.g. driving pressure and respiratory rate) [3–5], informing a more individualized treatment approach. A framework incorporating this multidimensional and dynamic perspective is, however, lacking and will likely provide a steppingstone for next developments.

Here, we propose an aviation-inspired safety framework to ventilation – "the Respiratory envelope" – that enables the incorporation of multiple, time-varying interactions between ventilator variables/settings and patient-specific, severity-dependent characteristics. This framework establishes the foundation for defining safe mechanical ventilation tailored to the individual patient and disease phase.

Inspiration by aviation

In developing this framework, we drew strong inspiration from aviation, which faced a similar challenge in the previous century where advances in aircraft technology and increasing needs for fast and long-haul transportation

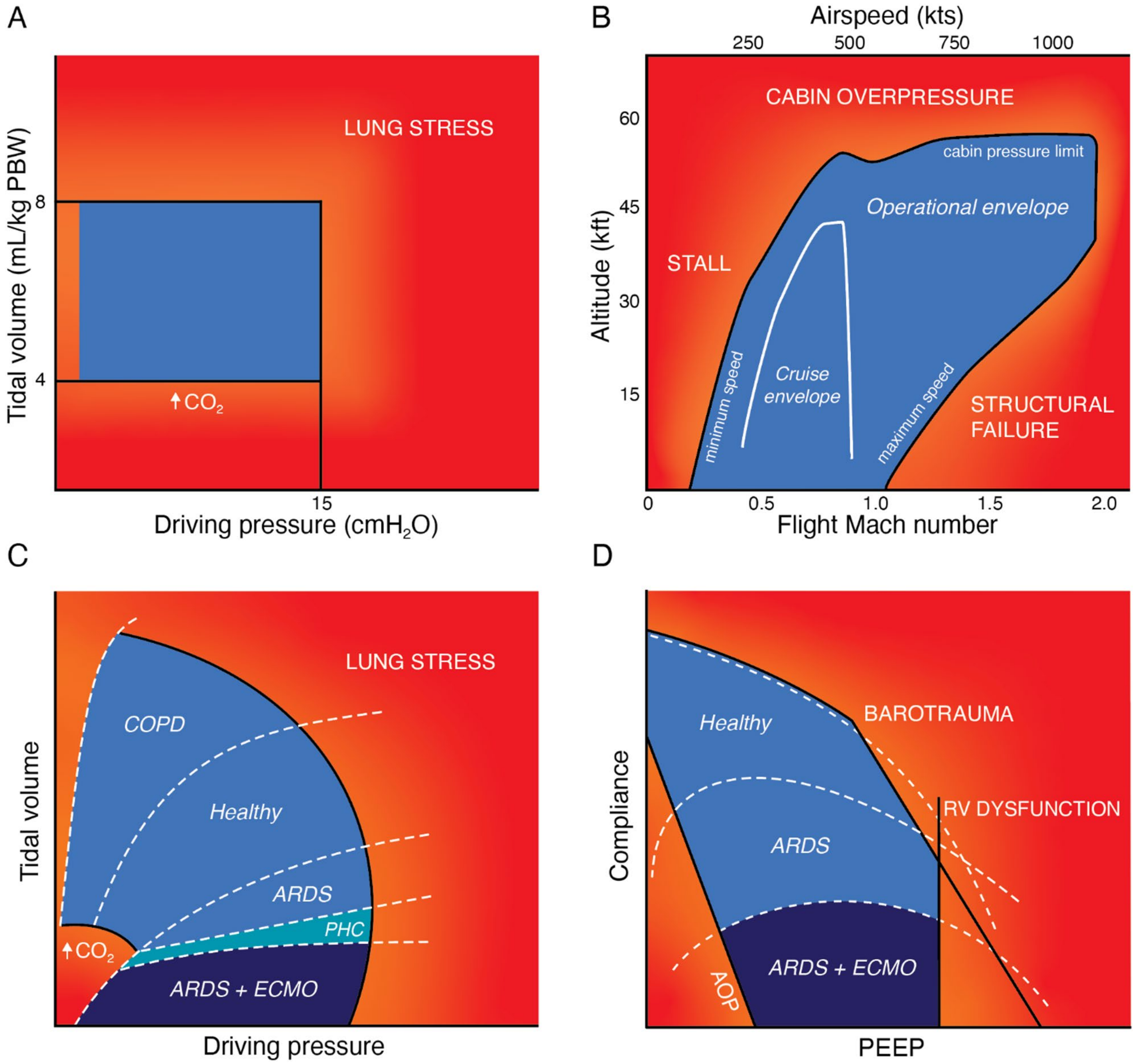

Fig. 1 Respiratory envelope heuristic conceptual framework and its inspiration and contemporary reference

and high maneuverability outpaced the ability of pilots to oversee and manage the accompanying risks. For instance, the Lockheed F-104 Starfighter, designed in the late 1950 s to achieve superior speed and altitude to excel in air-to-air combat, experienced serious safety issues, where almost one-third of the German fleet crashed and 116 pilots were killed, with loss of control cited as a major contributing factor [6]. These experiences prompted the development of fly-by-wire and autopilot systems which now control over 90% of commercial flight time and allow for unique flying capabilities of fifth generation fighter jets. These systems rely on fundamental information enclosed in the "flight envelope" (Fig. 1B) that transformed flight safety by defining aircraft- and flight phase-specific boundaries for safe operation [7]. Thresholds are defined as a function of (combinations of) flight altitude, airspeed, load factors and dynamic factors (e.g., wind gusts, undercarriage extension and flap deployment). For each aircraft, a unique envelope is established through calculations, followed by simulations and flight testing – starting from a known safe point within the envelope and systematically carefully exploring its boundaries in a process known as 'envelope opening'.

Respiratory envelope

We propose the "respiratory envelope" framework consisting of twelve interrelated variables (axes); (i) *tidal volume*, (ii) *driving pressure*, (iii) *positive end-expiratory pressure (PEEP)*, (iv) *respiratory rate*, (v) *plateau pressure*, (vi) *inspiratory-expiratory ratio*, (vii) *fractional inspiratory oxygen content* (FiO_2), (viii) *pleural pressure*, (ix) *compliance*, (x) *right ventricular function*, xi) *systemic oxygen consumption* (VO_2), and xii) *time*. Notably, these axes were selected on basis of their hypothetical contribution to risk patterns. In this context, risk encompasses a range of potential adverse effects, including insufficient gas exchange, overdistension, and derecruitment. Spontaneous breathing efforts were for example not incorporated as a separate axis as its effects seem mediated through pleural pressures and plateau pressures. The axes interdependence yields a twelve-dimensional envelope architecture, and the modular design of the framework would allow for expansion with potentially important upcoming parameters (e.g. diaphragmatic function). Likewise, the envelope framework would allow for simplification by omitting variables when evidence suggests no attributable effect.

While a full visualization of the respiratory envelope would be unfeasible, Fig. 1 depicts simplified two-dimensional heuristic conceptual envelope representations of tidal volume versus driving pressure (Fig. 1C) and compliance versus PEEP (Fig. 1D): blue denotes a safe zone, orange indicates relative risk, and red represents absolute risk for injury. Of note, all displayed boundaries are illustrative, simplified, non-linear, and highly dependent on e.g. chest wall mechanics, recruitability and regional heterogeneity. As cut-off values are still unknown and require prospective evaluation, we do not present axes units. In Fig. 1C, blue areas represent different patient scenarios (ARDS, healthy lung, COPD) depending on the compliance, with boundaries being delineated by the white dotted lines. In patients with ARDS (low compliance), maximum driving pressures are reached already with low tidal volumes. In healthy lungs and COPD, relatively higher tidal volumes can be accepted which occur at lower driving pressures; lung injury risks are therefore visualized as curved envelope boundaries. Lower boundaries reflect minimum tidal volumes required for gas exchange within safe boundaries for PaO_2 and $PaCO_2$. In ARDS, this limit can be lowered with permissive hypercapnia and applying veno-venous extracorporeal membrane oxygenation (ECMO), thereby expanding the operational envelope for lung protective ventilation. In this context, the acceptable upper limit for driving pressure should be reduced due to the increased risk of injury. In Fig. 1D, the left limit reflects the airway opening pressure (AOP) for the lowest PEEP that avoids repeated alveolar opening; this AOP likely depends on lung compliance (i.e., AOP would be higher in ARDS compared to normal lungs). In healthy lungs, maximal compliance is already achieved at low PEEP and additional PEEP could then cause overdistention. In ARDS, the optimal compliance occurs at higher pressures, with the shape of this curve depending on lung recruitability. The right boundary reflects risks of barotrauma due to overdistension, in combination with hemodynamic compromise because of high right ventricular afterload [8]. Higher compliant lungs may reach the barotrauma boundary at lower pressures as compared to stiff lungs, whereas in more severe ARDS right ventricular dysfunction may occur first. In patients with extremely low compliance or lung rest, addition of ECMO will open the envelope downwards.

Relevance of the respiratory envelope

Where current ventilation strategies insufficiently capture complex patient dynamics, the respiratory envelope framework enables personalized and dynamic treatment targets as a multi-objective optimization framework. Depending on the context, axes parameters could interchangeably function as controllable ventilator inputs, static variables or outcome/risk signals. This concept has thus far not been investigated, but there is an increasing interest in how ventilatory variables interact in their impact on patient outcomes (e.g. driving pressure and respiratory rate (4), and elastance versus tidal volume (5)), which is consistent with the "envelope paradigm". In addition, one study in mice even formulated a "safe region" as a function of tidal volume and PEEP [9].

We envision to operationalize this concept in future research and clinical practice through computational physiological models which could simulate real-time risks across a range of threshold combinations, based on continuously monitored, yet underutilized, physiological data, thereby defining the patient-specific envelope's boundaries [10]. These boundaries can then be validated in observational data and compared to current mechanical ventilation practices according to contemporary fixed thresholds. Boundaries and the location of the patient within the envelope will also vary over time as the disease progresses or improves, thereby altering the treatment response and requiring constant updating of models. As a "digital twin", the respiratory envelope framework could provide real-time, individualized decision support for clinicians. It may also drive the design of next-generation ventilators and software, enabling advanced features such as integrated heart–lung interaction or artificial intelligence-based closed-loop ventilation. In the long term, we envision interaction between different (e.g. hemodynamic and cerebral) envelopes, informing optimal parameter settings based on different organ needs. We also foresee the emergence of "respiratory envelope protection" algorithms, enabling the development of (semi-) automation of mechanical ventilation to keep patients within their envelope, thereby also reducing clinicians' workload. Analogous to the modern aviation systems that have dramatically improved flight safety, the respiratory envelope could revolutionize mechanical ventilation strategies to improve outcomes.

Conclusion

We propose the respiratory envelope as an innovative aviation-inspired framework to mechanical ventilation. This will enable continuously updated, patient-specific and disease-dependent calculations of safety limits across multiple interrelated dimensions to guide individual-tailored mechanical ventilation.

In current clinical practice, uniform cut-off values for driving pressure and tidal volume are recommended for all patients regardless of lung compliance or other physiological variables (1A). To refine this approach, we drew inspiration from aviation, where operational safety is defined by a "flight envelope" that maps safe limits across multiple dimensions. Figure 1B depicts a flight envelope for a supersonic aircraft where the left border is limited by stall speeds, which increase with altitude as air density decreases, and on the right boarder is delineated by maximum permissible airspeeds which are determined by engine performance and structural limits. Figure 1C presents an analogous, simplified respiratory envelope, depicting safe regions as a function of driving pressure and tidal volume. The lower boundary reflects the minimum tidal volume needed to meet VCO_2 clearance, assuming that other parameters relevant to minute volume (e.g. dead space, respiratory rate, and ECMO related parameters) remain constant. In practice, however, changes in these parameters would dynamically shift these thresholds. The left boundary reflects that a minimum driving pressure is required to generate a certain tidal volume, acknowledging that this may change in the presence of spontaneous breathing and also depends on the elastance ratios between the lungs and chest wall. The upper and right boundaries indicate the risk of ventilator-induced lung injury due to excessive volumes and/or pressures. These safe regions shift with lung compliance. The white dotted lines indicate the boundaries between different conditions, illustrated here for COPD, healthy lungs, and ARDS. VV-ECMO can further reduce or eliminate the tidal volume required for CO_2 removal. Figure 1D extends this framework to PEEP and compliance, with the left boundary defined by airway opening pressure and the right boundary by risks of barotrauma and hemodynamic compromise. To note, low PEEP can also lead to hemodynamic compromise in ARDS, requiring an additional left boundary line when appropriate. Hypothetical optimal compliance across PEEP levels is shown for healthy lungs and ARDS, with or without ECMO (white dotted lines). In all panels, blue denotes a safe zone, orange indicates relative risk, and red represents absolute risk for injury. Notably, no units of measurement are shown for panels C and D, as cut-off values are still unknown.

Abbreviations

AOP	Airway opening pressure
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
VV ECMO	Veno-venous extracorporeal membrane oxygenation
PEEP	Positive end-expiratory pressure
PHC	Permissive hypercapnia
PBW	Predicted body weight
RV	Right ventricle

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Author contributions

CM: hypothesis generation, conceptualization, writing; EO: conceptualization, writing; PS: conceptualization, writing; LH: conceptualization, writing; JAM: conceptualization, writing; AHJ: conceptualization, writing, illustration.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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