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LASTING LEGACY IN INTENSIVE CARE MEDICINE

Protective ventilation

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Following the initial observation in animal models as early as 1967, a key paper in 1974 demonstrating that high inspiratory pressures caused lung injury [1] (Fig. 1), crystallized the recognition that mechanical ventilation itself can harm the lung. Experimental models were also instrumental in showing that cyclic lung re-opening and closing creates shear stress with alveolar injury, which could be prevented by the application of positive end-expiratory pressure (PEEP) [2]. The use of computed tomography showed the response to PEEP in terms of recruitment of lung volume, giving rise to the 'baby lung' concept in acute respiratory distress syndrome (ARDS) [3]. Experimental models were also helpful in determining that it was not inspiratory pressure per se, but rather over-distention that caused harm leading to the concept of 'volutrauma' [4]. These findings led to the 'open lung' concept [5], which argues that a ventilation approach that prioritizes maintenance of lung volume would avoid the lung injury resulting from shear stress. Also, the concept of 'biotrauma' was demonstrated in an experimental model [6], whereby high-stretch ventilation generates the release of inflammatory mediators from the lung, leading to systemic inflammation and distal organ injury, particularly in the presence of zero PEEP. Two years later, these findings were validated clinically in ARDS patients.

In the early 1990s, these laboratory insights were followed up by observations that low tidal volume ventilation while disregarding the concurrent hypercapnia, seemed to improve outcome [7]. This concept of 'permissive hypercapnia' underlined the rationale of limiting intensity of mechanical ventilation and inspired the design of the pivotal ARDS Network ARMA trial [8]. In this trial, a 'lung-protective' strategy [tidal volume (V_T) of 6 ml/kg and a plateau pressure of 25–30 cmH_2O] was compared with traditional V_T of 12 ml/kg. A low V_T strategy reduced absolute mortality by 9%, ushering in the era of 'lung protective' ventilation in ARDS. It took roughly another 15 years before it was demonstrated that application of low V_T also benefitted patients without ARDS.

Our understanding of what constitutes 'protective ventilation' continued to evolve. The clinical use of oesophageal balloon catheters allowed estimation of trans-pulmonary pressure by quantifying the contribution of extra-thoracic elements (chest wall, abdomen) to ventilation pressures. In a small physiologic trial in ARDS patients, the use of oesophageal pressures to set PEEP significantly improved oxygenation and compliance compared to a standard approach with a PEEP table [9]. The concept of lung 'stress and strain' followed, as trans-pulmonary pressure could be used to assess the force applied to the lung during mechanical ventilation — the so-called lung parenchymal stress. Lung strain refers to the associated deformation of the lung in response to the applied stress and is computed as the change in lung volume as a proportion of functional residual capacity (ΔV/FRC). A key insight is that injurious levels of stress and strain may occur even during application of standard 'protective' ventilatory settings. Bedside application of this concept can be done with the 'stress index', which is assessed by examining the pressure–time curve during a constant inspiratory flow [10]. Additionally, it was demonstrated that driving pressure (ΔP = plateau pressure – PEEP) was a more robust determinant of mortality risk than inspiratory pressure or V_T, and that decreases in ΔP resulting from optimization of ventilator settings were associated with increased survival in a mediation analysis [11].

The optimal goals of setting of the ventilator continue to be refined as new insights emerge. The 'open lung' concept was challenged using an experimental model of

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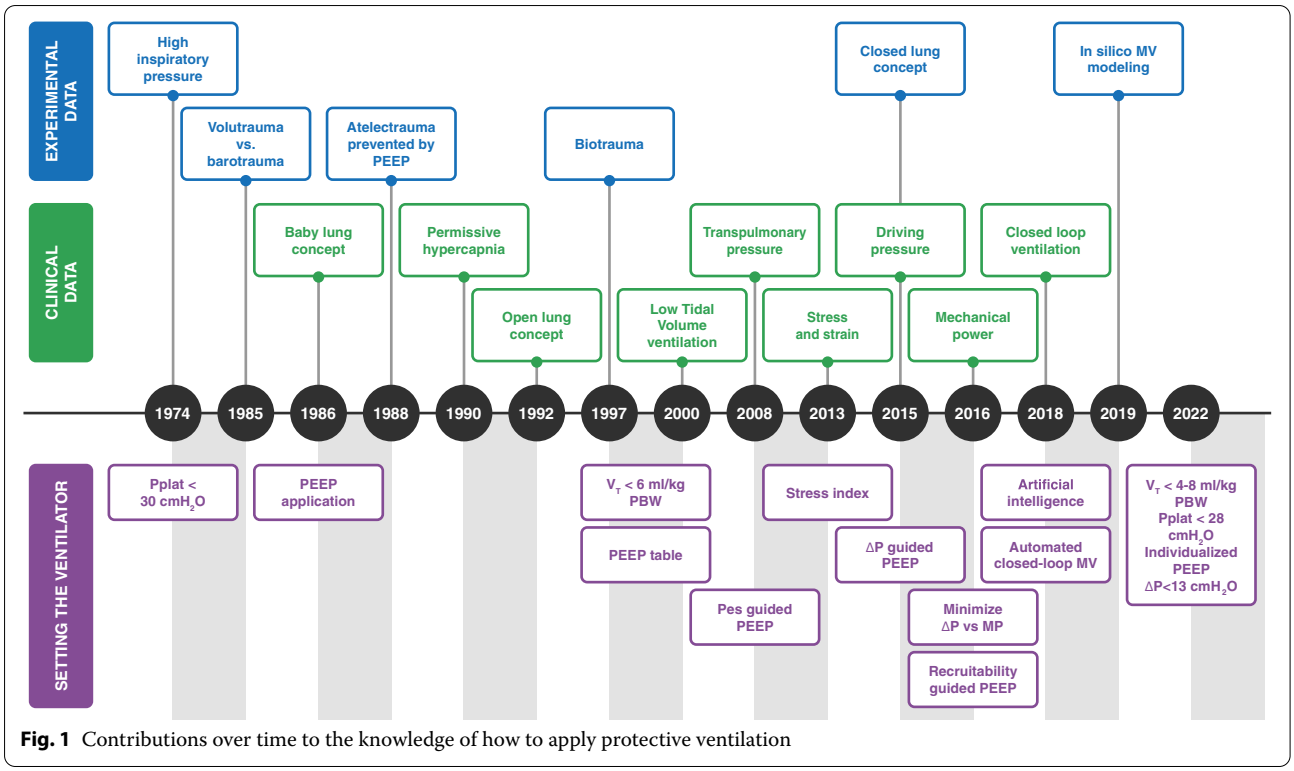

Fig. 1 Contributions over time to the knowledge of how to apply protective ventilation

ARDS, in which combination of low tidal volume and low PEEP with associated low driving pressure and alveolar collapse, resulted in a reduction of stress and lung injury [12]. This strategy of keeping the collapsed lung closed is also known as 'permissive atelectasis'.

Taken together, these concepts move beyond standard protective ventilation settings toward individualized mechanical ventilation. By now it is clear that both static (tidal volume, PEEP, plateau pressure, trans-pulmonary driving pressure) and dynamic parameters (respiratory rate, inspiratory and expiratory airflow) are implicated in the pathophysiology of ventilator induced lung injury (VILI). This is reflected in the concept of 'mechanical power' which aims to quantify the total amount of energy delivered during mechanical ventilation, defined as the sum of the degree of strain per cycle and the duration of exposure. The accepted goal is now to impart the least mechanical power possible to mitigate the risk of VILI [13], while achieving adequate gas exchange. The vulnerability of lung tissue to mechanical stress and strain also plays a role. Since lungs behave as a viscoelastic system, the components of the extracellular matrix require time to adapt to each ventilator variable, suggesting that setting adjustments should preferably be done in small increments or decrements. Of note, these insights have evolved mostly from studies in patients with injured lungs. Thereby, the optimal settings for those with normal compliant lungs may differ from those with ARDS. Perhaps in line with this, is the observation in the ARDSnet tidal volume study, that there was no benefit of lower V_T in those patients with the highest compliance.

As lung injury evolves, the insult inflicted by mechanical ventilation can change over time, requiring constant re-evaluation of settings. Closed-loop ventilation modes automatically adjust settings based on physiologic signals and patient activity, thus requiring fewer manual interventions while delivering safe ventilation [14].

Implications for clinical practice

As VILI importantly impacts outcome of mechanically ventilated patients, even in those without lung injury, it follows that those caring for the critically ill should apply protective ventilatory settings to the best of their abilities. This is feasible, without the need for advanced monitoring systems, but by appreciation of the concepts as summarized here. The field of protective ventilation will continue to evolve as we generate new insights in the laboratory and in the clinics. A promising novel innovation is the use of in silico computational models of critically ill ARDS patients [15], which most likely will inform us on how to further refine ventilator settings. In addition, such refinements can potentially be done around the clock, instead of only during ward rounds. Moreover, functional imaging modalities may be useful to help set the

ventilator. Although robust data of benefit are still lacking, electrical impedance tomography, for instance, can provide imaging of regional air distribution in the lungs.

Our exciting journey continues, and we are not there yet!

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Declarations

Conflicts of interest
JGL reports receiving consultancy fees from Glaxosmithkline and Baxter Corporation. The other authors have no competing interests to report.

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References

1. Webb HH, Tierney DF (1974) Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565
2. Sandhar BK, Niblett DJ, Argiras EP, Dunnill MS, Sykes MK (1988) Effects of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. Intensive Care Med 14:538–546
3. Gattinoni L, Presenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, Scarani F, Marcolin R, Cappelletti G (1986) Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imaging 1:25–30
4. Hernandez LA, Peevy KJ, Moise AA, Parker JC (1989) Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol (1985) 66:2364–2368
5. Lichtwarck-Aschoff M, Nielsen JB, Sjostrand UH, Edgren EL (1992) An experimental randomized study of five different ventilatory modes in a piglet model of severe respiratory distress. Intensive Care Med 18:339–347
6. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952
7. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372–377
8. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
9. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH (2008) Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 359:2095–2104
10. Terragni PP, Filippini C, Slutsky AS, Birocco A, Tenaglia T, Grasso S, Stripoli T, Pasero D, Urbino R, Fanelli V, Faggiano C, Mascia L, Ranieri VM (2013) Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. Anesthesiology 119:880–889
11. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG (2015) Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 372:747–755
12. Samary CS, Santos RS, Santos CL, Felix NS, Bentes M, Barboza T, Capelozzi VL, Morales MM, Garcia CS, Souza SA, Marini JJ, Gama de Abreu M, Silva PL, Pelosi P, Rocco PR (2015) Biological impact of transpulmonary driving pressure in experimental acute respiratory distress syndrome. Anesthesiology 123:423–433
13. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, Chiumello D, Quintel M (2016) Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 42:1567–1575
14. Arnal JM, Garnero A, Novotni D, Corno G, Donati SY, Demory D, Quintana G, Ducros L, Laubscher T, Durand-Gasselin J (2018) Closed loop ventilation mode in Intensive Care Unit: a randomized controlled clinical trial comparing the numbers of manual ventilator setting changes. Minerva Anestesiol 84:58–67
15. Saffaran S, Das A, Hardman JG, Yehya N, Bates DG (2019) High-fidelity computational simulation to refine strategies for lung-protective ventilation in paediatric acute respiratory distress syndrome. Intensive Care Med 45:1055–1057