

RESEARCH FINGERPRINT

IDENTIFIER

LJMHR-226753

PEER REVIEW

Double Blind

SIMILARITY CHECK

Perplexity AI and iThenticate

ACCESS

Open Access

LANGUAGE

English

PRINT ISSN

2515-5784

ONLINE ISSN

2515-5792

EDITION

ABBREVIATION

LJMHR

VOLUME

26

ISSUE

4

YEAR

2026

KEY DATES

RECEIVED

2026-04-03

ACCEPTED

2026-04-13

ONLINE PUBLISHED

2026-05-21

PUBLISHED

2026-06-17

CATALOGING

CROSSMARK DOI

10.34257/LJMHR226753UK

MESH CLASS

D001237, D011175, D001281,  
D011187

ICD CLASS

J98.1

UDC CLASS

612.2

Article Record

# The Paradox of Airway Closure: From Protection to Pathology

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ABSTRACT

Airway closure, first recognized by Laennec and later quantified in studies by Dollfuss, Hedenstierna and Hughes, represents a physiological phenomenon with far-reaching clinical consequences. While often overlooked in critical care, its role in promoting atelectasis, impaired gas exchange, and ventilator-induced lung injury is well established. The present narrative review revisits the fundamental physiology of airway closure, its exacerbation in anaesthesia and obesity, and its near-universality in mechanically ventilated ARDS patients. A reinterpretation of pleural pressure data from landmark studies, suggests that airway closure may be far more prevalent than currently appreciated. Strategies such as optimal PEEP and avoidance of high oxygen fractions are discussed, with emphasis on the urgent need for better integration of airway closure physiology into clinical practice. This article re-examines how positive airway pressure in combination with elevated intrathoracic pressure — the inevitable companion of positive pressure ventilation — underlies many of the adverse effects attributed to modern mechanical ventilation. By contrast, negative pressure ventilation, long abandoned, may offer physiological advantages worth reconsidering. The question we must now ask is: could a return to negative extra-thoracic pressure — or a hybrid model — prevent the very complications we have come to accept as inevitable?

Index Terms: Mechanical Ventilation • Positive Pressure Ventilation • Negative Pressure Ventilation • Airway Resistance • Airway Closure • Atelectasis • Ventilator Induced Lung Injury • Pleural Pressure • Intra-thoracic pressure

FUNDING

No external funding was declared for this work.

CONFLICTS

The authors declare no conflict of interest.

AI USAGE

No generative AI was used for analysis or results.

HOW TO CITE

van Egmond et al. (2026). The Paradox of Airway Closure: From Protection to Pathology. London Journal of Medical and Health Research, 26(4), 10-17. DOI: 10.34257/LJMHR226753UK




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ONLINE



**METADATA CONTINUATION**

**AUTHOR CONTACT QR LEDGER**

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**ARCHIVAL RECORD**

## NARRATIVE REVIEW

# The Paradox of Airway Closure: From Protection to Pathology

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## Abstract

Airway closure, first recognized by Laennec and later quantified in studies by Dollfuss, Hedenstierna and Hughes, represents a physiological phenomenon with far-reaching clinical consequences. While often overlooked in critical care, its role in promoting atelectasis, impaired gas exchange, and ventilator-induced lung injury is well established. The present narrative review revisits the fundamental physiology of airway closure, its exacerbation in anaesthesia and obesity, and its near-universality in mechanically ventilated ARDS patients. A reinterpretation of pleural pressure data from landmark studies, suggests that airway closure may be far more prevalent than currently appreciated. Strategies such as optimal PEEP and avoidance of high oxygen fractions are discussed, with emphasis on the urgent need for better integration of airway closure physiology into clinical practice. This article re-examines how positive airway pressure in combination with elevated intrathoracic pressure — the inevitable companion of positive pressure ventilation — underlies many of the adverse effects attributed to modern mechanical ventilation. By contrast, negative pressure ventilation, long abandoned, may offer physiological advantages worth reconsidering. The question we must now ask is: could a return to negative extra-thoracic pressure — or a hybrid model — prevent the very complications we have come to accept as inevitable?

**Keywords:** Mechanical Ventilation, Positive Pressure Ventilation, Negative Pressure Ventilation, Airway Resistance, Airway Closure, Atelectasis, Ventilator Induced Lung Injury, Pleural Pressure, Intra-thoracic pressure

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## 1 Introduction

Despite decades of technical progress in mechanical ventilation, an important mechanical consequence of positive pressure ventilation (PPV) remains insufficiently appreciated: the rise in pleural pressure ( $P_{pl}$ ) and intrathoracic pressure ( $P_{it}$ ) that inevitably accompanies the application of positive airway pressure ( $P_{aw}$ ) within a thorax that does not actively expand. This increase in surrounding tissue pressure may compress the lung parenchyma and the small peripheral airways, particularly in dependent regions or in lungs with reduced compliance.

The present article is not intended as a comprehensive review of airway closure or ventilator-induced lung injury (VILI). Rather, it focuses on a specific mechanical interpretation: that airway closure, atelectasis, hyperinflation, and related complications during PPV are closely linked to lung tissue compression caused by elevated pleural and intrathoracic pressure. This perspective differs from the common emphasis on transpulmonary pressure alone, suggesting that reductions in transpulmonary pressure by themselves are insufficient to explain or prevent atelectasis during positive-pressure ventilation.

The transition from negative pressure ventilation (NPV) to PPV in the mid-20th century was driven largely by practical advantages—

airway access, emergency applicability, and ease of use—rather than by controlled physiological comparison. As a result, the mechanical differences between inflating the lung by raising  $P_{aw}$  and inflating it by lowering  $P_{pl}$  may have remained underappreciated. The present review reconsiders airway closure in that light.

## TRIBUTE TO PROFESSOR HEDENSTIERNA

The ideas presented in this paper have been profoundly influenced by the pioneering work of Göran Hedenstierna, whose studies from the 1970s onward laid much of the foundation for our current understanding of airway closure, atelectasis, and the effects of oxygen and pressure on lung mechanics.

Those who met Göran (JPM) may recall his persistent warning against the routine use of high oxygen concentrations during PPV. He repeatedly emphasized the relationship between inspired oxygen fraction and the development of atelectasis. At the time, however, few of us fully understood the mechanism he proposed, and clinical practice changed little—we continued to increase the oxygen concentration to 100% before intubation and before terminating PPV and proceeding to extubation.

When I (JvE) revisited his 1976 paper on airway closure [1], I realized how far ahead of his time he had been. He recognized that airway closure is not merely a pathological phenomenon, but a physiological mechanism that protects the lung at low volumes. His meticulous experiments demonstrated how anaesthesia, PPV, and high oxygen concentrations disturb this delicate balance and thereby promote atelectasis.

“This concept is increasingly reflected in contemporary lung-protective strategies, which recommend avoiding unnecessarily high inspired oxygen fractions. During maintenance, weaning, and immediately prior to extubation,  $\text{FiO}_2$  may often be limited to approximately 0.4 whenever clinically feasible, whereas higher  $\text{FiO}_2$  values, up to approximately 0.8, may be appropriate during induction and airway management [2].”

In addition, positive pressure ventilation differs fundamentally from spontaneous breathing and NPV in its hemodynamic effects. The increase in intrathoracic pressure reduces venous return and cardiac preload, may impair cardiac output, and can transiently affect organ perfusion, for example by reducing urine output. At the same time, it decreases left ventricular afterload while increasing right ventricular afterload through elevated pulmonary vascular resistance.

In May 2021, I wrote to Professor Hedenstierna to share my reflections on the contemporary implications of his work, unaware that my letter would reach him only weeks before his passing. I am convinced that, had our paths crossed earlier, we would have found substantial common ground.

This paper therefore stands, in part, as a continuation of his line of reasoning—exploring how  $P_{pl}$ ,  $P_{it}$ , and airway closure interact to shape both ventilation and perfusion. His scientific legacy remains a source of insight for those who seek to understand and preserve the lung’s intrinsic physiology rather than override it.

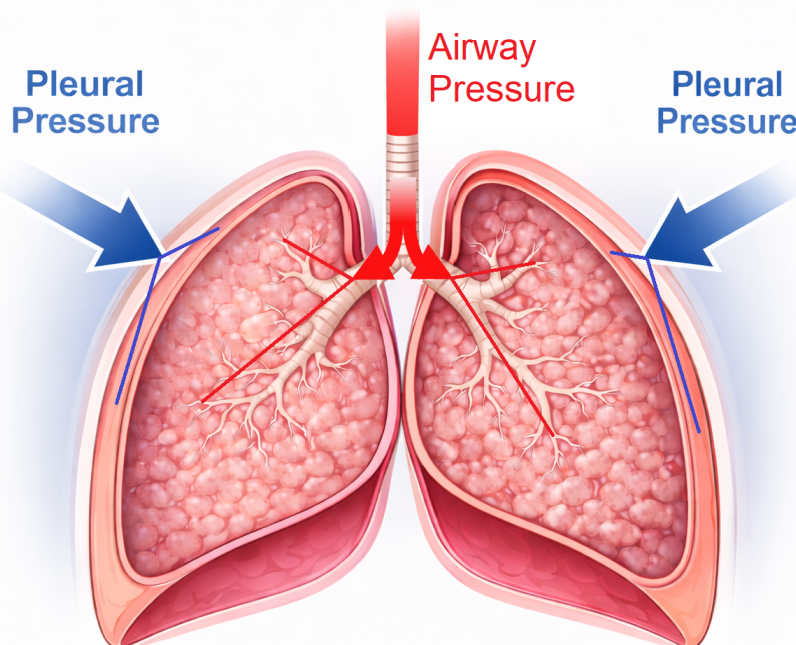
## 2 Mechanical Framework

The lung parenchyma is mechanically interposed between the pleural space and the conducting airways (Figure 1).  $P_{pl}$  acts on the external surface of the lung, whereas  $P_{aw}$  is transmitted through the bronchial tree into the alveolar space. Both therefore contribute to the pressure environment surrounding the small intraparenchymal airways, particularly the terminal and respiratory bronchioles—highly compliant, collapsible structures of submillimeter diameter that supply individual acini.

For this reason, lung tissue compression cannot be understood from transpulmonary pressure alone. Transpulmonary pressure ( $P_{tp}$ ), defined as alveolar pressure ( $P_{alv}$ ) minus  $P_{pl}$  (in contrast to the very commonly used definition:  $P_L = P_{aw}$  minus  $P_{pl}$ . The two definitions are only equivalent in the absence of airway closure.), describes distending pressure across the lung, but does not by itself describe the absolute pressure acting on the parenchyma. A useful approximation of the compressive load on the parenchyma is the mean of  $P_{aw}$  and  $P_{pl}$ :

$$P_{it} \approx (P_{aw} + P_{pl})/2. \quad (1)$$

When  $P_{aw}$  and  $P_{pl}$  rise simultaneously,  $P_{tp}$  may remain unchanged while the absolute pressure surrounding the parenchyma increases. Under such conditions, small compliant airways embedded in lung tissue may narrow or close, especially in gravity-dependent regions, where the weight of the overlying lung tissue increases local compressive forces, an effect that may be further enhanced in the presence of edema. This distinction helps explain why PPV and NPV cannot be considered mechanically equivalent even at similar  $P_{tp}$ ’s.



**Figure 1.** Pressures acting on the lung parenchyma during positive and negative pressure ventilation, the parenchyma is sandwiched between pleural space and the main airways. During positive pressure ventilation, airway pressure is elevated above atmospheric pressure and pleural pressure rises in parallel. During negative pressure ventilation, pleural pressure is reduced below atmospheric pressure (i.e., becomes more negative), while airway pressure remains at atmospheric level. Airway pressure is transmitted throughout the bronchial tree into the alveolar space and therefore contributes directly to the mechanical compression experienced by the lung tissue.

### 3 Physiological Airway Closure

Airway closure is a well-established physiological phenomenon. In patients with small airway disease, peripheral airway closure becomes evident during forced expiration, as demonstrated by expiratory CT imaging, in which air trapping and mosaic attenuation are recognized as indirect markers of small-airway closure [3]. Milic-Emili, in his 2007 review [4], recalled that René Laennec had already described “trapped air” in the excised lung around 1820. Dollfuss et al. [5] demonstrated that expiration below functional residual capacity (FRC) initiates airway closure, and Hughes et al. [6] confirmed this in the excised dog lung. According to these classical observations, closure of the feeding airway occurs when local trans-airway pressure falls below a threshold of about 2–2.5 cmH<sub>2</sub>O.

This mechanism protects the alveolus against complete collapse: the small airway closes before the alveolar unit itself is fully compressed. In the healthy spontaneously breathing subject, such closure is common and usually transient and reversible. Excluded units are readily reintegrated during the next inspiration or spontaneous sigh, preserving ventilation–perfusion matching and lung volume stability.

Because  $P_{pl}$  becomes less negative toward the dependent regions of the lung, closure begins in the dependent lung and progresses upward as  $P_{pl}$  rises or lung volume falls. This gravitational dependence is reflected in the classic concepts of closing volume and closing capacity [7].

This gravitational sequence is also directly reflected in the lower, leftward limb of the pressure–volume relationship. As lung volume decreases below FRC, progressively more dependent airways reach their closing threshold, resulting in a gradual loss of ventilated units over a pressure range that corresponds to the vertical  $P_{pl}$  gradient. The residual volume thus represents the lung volume at which airway

closure has extended throughout the lung. At still lower pressures, this volume remains trapped (as noticed by Laennec), since the closed airways prevent further emptying.

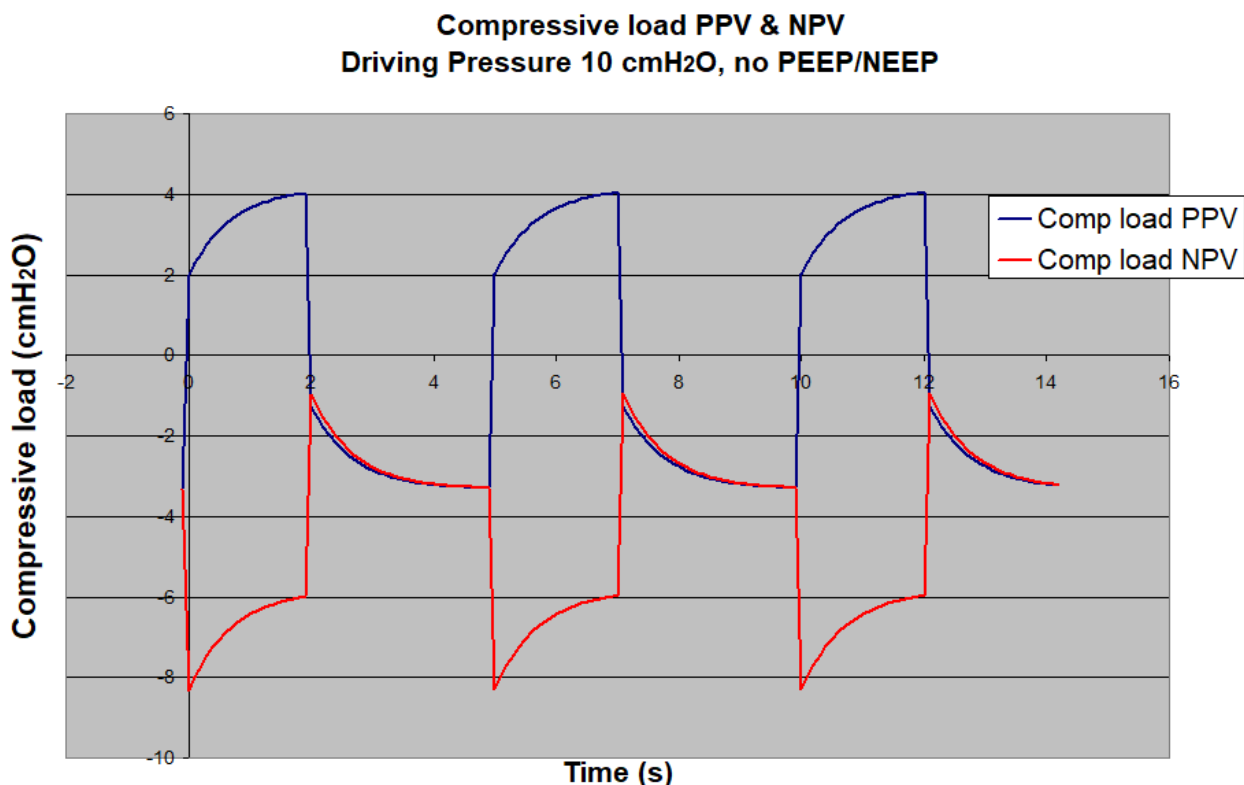
#### COMPRESSIVE LOAD DURING INSPIRATION: WHY PPV MAY TURN PHYSIOLOGY INTO PATHOLOGY

Figure 2. illustrates the simulated compressive load on lung parenchyma by PPV and NPV, both applied with an identical driving pressure of 10 cmH<sub>2</sub>O and zero end-expiratory pressure. Although resulting volume changes may be (they are not! See below under “Experimental support from isolated lungs”) comparable, the underlying pressure environment differs fundamentally.

The simulation shown in Figure ?? is based on a simplified lumped-parameter model of the respiratory system, consisting of a single-compartment lung enclosed within a compliant chest wall. Both lung and chest wall compliances were assumed to be linear and equal (150 mL/cmH<sub>2</sub>O), with a functional residual capacity (FRC) of 2.4 L and a pleural pressure of -6 cmH<sub>2</sub>O at FRC.

The model was not intended to represent regional heterogeneity or complex lung mechanics, but rather to illustrate the effect of different pressure application modes on the mechanical environment of the lung. In particular, the simulation highlights how airway pressure contributes to parenchymal compression during PPV, whereas NPV alters the surrounding pressure without increasing airway pressure.

In the absence of PEEP or negative end-expiratory pressure (NEEP), expiratory curves for PPV and NPV are nearly superimposed. However, when PEEP or NEEP is introduced, the curves diverge, reflecting differences in the pressure environment during both inflation and deflation.



**Figure 2.** Compressive load on parenchyma during mechanical ventilation. The load is depicted during both NPV and PPV, with a driving pressure of 10 cmH<sub>2</sub>O ( $\approx 10$  mbar). Here no PEEP (NEEP for NPV) is applied, that is why the expiration curves are identical (the slight differences are due to the simulation process:  $\Delta t \rightarrow 0$  would make them coincide perfectly). PEEP will shift the curve upward for PPV and down for NPV and make this equivalence disappear.

Compressive load is approximated as the mean  $P_{it}$ , here defined as  $(P_{aw} + P_{pl})/2$ . During inspiration with NPV,  $P_{pl}$  becomes more negative, reducing this mean pressure and thereby decreasing tissue compression. In contrast, during PPV,  $P_{aw}$  rises above atmospheric pressure and  $P_{pl}$  increases accordingly, resulting in an increase in compressive load during inspiration.

This difference has major consequences for small peripheral airways. Under physiological conditions, airway closure during expiration is typically transient and reversible. However, under PPV—particularly in dependent regions—closed airways may fail to reopen during the subsequent inspiration, because the rise in  $P_{aw}$  is accompanied by an increase in surrounding tissue pressure.

Airway hysteresis, partly related to surface tension and adhesive forces at the airway walls, ongoing gas absorption, and the absence of sufficiently negative  $P_{pl}$  interact to stabilize airway closure. Hysteresis implies that reopening requires higher distending pressures than those present at end-expiration, while ongoing gas absorption further reduces the volume of isolated acini, particularly at high inspired oxygen fractions. In the absence of sufficiently negative  $P_{pl}$  to relieve surrounding tissue compression, these regions may remain closed despite apparently adequate transpulmonary pressure. Thus, a normally protective physiological mechanism may evolve into a pathological state characterized by persistent exclusion of peripheral lung units, impaired recruitment, and progressive atelectasis.

From a clinical perspective, this has important implications for the interpretation of  $P_{es}$  measurements. In routine practice, transpulmonary pressure is estimated as  $P_{aw} - P_{es}$ , assuming that  $P_{aw}$  is transmitted to the alveoli. However, this assumption no longer holds once peripheral airway closure occurs e.g. during expiration. At the moment of closure, alveolar pressure in the affected units equals the  $P_{aw}$  at which flow ceases locally, after which these units become mechanically uncoupled from the airway opening. Subsequent decreases in  $P_{aw}$  are therefore not transmitted to these regions. As a result, a transpulmonary pressure calculated from  $P_{aw}$  and  $P_{es}$  may not reflect the local mechanical conditions within closed or excluded lung units. Airway opening pressure (AOP), typically assessed during inspiration, provides information on reopening but does not capture the alveolar pressure at which closure occurred during expiration.

This mechanism helps explain why airway closure is frequently observed in anaesthetized and mechanically ventilated patients, particularly in conditions associated with elevated  $P_{pl}$ , such as obesity, ARDS, reduced chest wall compliance, pneumoperitoneum, and Trendelenburg positioning.

It should be emphasized that this expression represents a global or mean approximation of the pressure acting on the lung parenchyma. While  $P_{aw}$  is relatively uniform throughout the lung at a given moment,  $P_{pl}$  exhibits substantial regional variation, primarily due to gravitational effects and the weight of overlying lung tissue. This results in a vertical gradient of parenchymal compression, with higher compressive forces in dependent regions and lower values in non-dependent regions.

This spatial heterogeneity is further amplified in the presence of lung injury, edema, or regional stiffening, where local mechanical conditions may deviate markedly from the mean estimate. Consequently, the compressive load on the parenchyma is not uniform, but greatest in dependent regions, where airway closure is also most likely to occur.

In this context, the approximation  $P_{it} \approx (P_{aw} + P_{pl})/2$  should be interpreted as a conceptual framework rather than an exact local descriptor of pressure transmission. This limitation does not diminish the relevance of the concept itself, but rather highlights that its clinical implications are most pronounced in dependent lung regions, where pleural pressure, and thus parenchymal compression, is highest.

## 4 Experimental Support from Isolated Lungs

Direct mechanical support for this concept comes from isolated-lung experiments comparing PPV and NPV. Klassen et al. [8] and Eckert et al. [9] ventilated excised lungs either by applying positive pressure at the airway opening or by applying negative pressure externally around the lung.

Klassen et al. [8] showed that, for a given tidal volume, PPV required approximately twice the driving pressure needed during NPV. This already suggested greater internal flow limitation during PPV. Even more striking was their observation that a small peripheral defect at the lung surface leaked almost five times more during NPV than during PPV at comparable tidal volumes. Eckert et al. [9] reported concordant findings.

The interpretation is straightforward. During NPV, peripheral regions remain ventilated and in communication with the airway tree, allowing gas to reach and escape through the peripheral defect. During PPV, by contrast, the much smaller leakage indicates that the distal lung is poorly ventilated or functionally excluded. These experiments therefore provide direct evidence that PPV promotes peripheral airway narrowing or closure, whereas NPV preserves distal airway patency.

## 5 Clinical Analogue: Delayed Pneumothorax

A similar phenomenon appears to occur clinically in delayed pneumothorax during PPV. In a recent case report [10], a pneumothorax remained occult during ongoing PPV and became apparent only after the patient resumed spontaneous breathing.

This behaviour mirrors the isolated-lung findings. During PPV, elevated  $P_{aw}$  and  $P_{pl}$  increase parenchymal compression, so that a pleural defect in a poorly ventilated peripheral region may not communicate effectively with the central airways. Air leak into the pleural space then remains limited, and pneumothorax may not become clinically evident. When spontaneous breathing resumes,  $P_{pl}$  becomes more negative, peripheral airways reopen, and the distal defect again communicates with the airway tree. The pneumothorax then declares itself.

Thus, delayed pneumothorax can be understood as an *in vivo* counterpart of the reduced peripheral leak observed during PPV in isolated lungs [8,9].

## LESSONS FROM COPD: AVOIDANCE OF COMPRESSIVE LOADING

The mechanical consequences of elevated  $P_{it}$  are well illustrated in patients with chronic obstructive pulmonary disease (COPD). These patients characteristically avoid forceful expiration, as increased  $P_{pl}$  leads to airway narrowing and premature closure of small airways. Instead, they adopt a breathing pattern with prolonged, low-flow expiration and often operate at an increased end-expiratory lung volume.

By elevating FRC, COPD patients maintain airway patency and reduce airway resistance, thereby minimizing the compressive effects of  $P_{it}$  on peripheral airways. This adaptive strategy reflects an intuitive avoidance of the very mechanism that may be imposed during PPV.

In this context, PPV—by increasing  $P_{pl}$  and  $P_{it}$  during inspiration—may counteract these protective adaptations, promoting airway closure and increasing resistance, particularly in already vulnerable lung regions [11].

## 6 PEEP: Stabilization and Compression

The effects of positive end-expiratory pressure (PEEP) require careful interpretation. PEEP is often described as “recruiting” the lung, but its action is mechanically dual.

On the one hand, PEEP raises  $P_{aw}$  and thereby raises  $P_{it}$ , which increases compressive loading of the parenchyma, especially in dependent regions. On the other hand, the resulting increase in lung volume enlarges airway caliber and may stabilize small airways against collapse. Because airway resistance decreases strongly with airway radius, this volume effect can be substantial.

The apparent benefit of PEEP may therefore reflect geometric expansion and airway stabilization rather than true relief of tissue compression. The net effect depends on the balance between increased absolute pressure and increased lung volume. This duality may help explain why PEEP sometimes improves oxygenation and compliance while not necessarily reversing the underlying compressive mechanism.

### 6.1 Flow Dependence of Airway Closure

Airway closure is influenced not only by static pressure levels but also by the temporal pattern of pressure application. Because different lung regions have different time constants, rapid inspiration preferentially fills units with short time constants, typically more central or less compressed regions.

During fast inspiration, proximal units fill early and raise pleural and parenchymal pressure before more distal regions have had time to fill. This early rise in  $P_{it}$  may further compress peripheral airways, making the distal lung progressively less accessible during the same breath. In contrast, a more gradual flow profile allows distal regions more time to fill before compressive forces increase.

This concept offers a plausible mechanical explanation for the benefits reported with flow-controlled strategies. Flow-controlled expiration (FLEX) [12] reduces rapid pressure decline during expiration and may thereby limit derecruitment. Likewise, regulated inspiratory and expiratory flow, as used in devices such as the EVONE ventilator [13], may promote more homogeneous distribution of ventilation by avoiding abrupt pressure changes.

## 7 Clinical Evidence: Obesity, ARDS, and AOP

Clinical observations also support a major role of elevated  $P_{pl}$  in airway closure. In supine obesity, increased abdominal pressure displaces the diaphragm cranially and raises  $P_{pl}$ . Behazin et al. [14] described complete airway closure under such conditions, with inspiratory flow appearing only after  $P_{aw}$  exceeded the AOP.

AOP is a useful physiological marker, but it should not be interpreted too simplistically. The measured AOP most likely represents the pressure at which the first previously closed regions reconnect with the central airways, not the pressure at which the entire lung has reopened. Because  $P_{pl}$  varies substantially from non-dependent to dependent lung, reopening must be expected to proceed gradually over a pressure range.

Thus, the presence of an AOP confirms airway closure, but the absence of a clearly measurable AOP does not exclude it. If PEEP is already close to or above the opening pressure of the least dependent regions, flow may appear immediately during inspiration as  $P_{aw}$  rises, even though much of the lung was initially functionally closed. This distinction is important in obesity and ARDS, [15,16] where elevated  $P_{pl}$  may cause widespread airway closure without a dramatic or easily recognized AOP.

## PLEURAL PRESSURE, THORACIC VOLUME, AIRWAY CLOSURE AND THE “BABY LUNG” IN ARDS

As emphasized by Grasso [17], the reduced compliance of the respiratory system in ARDS may arise from either the lung or the chest wall. Distinguishing between these requires knowledge of  $P_{pl}$ , which can be estimated from oesophageal pressure measurements. Several studies have applied this approach to guide ventilator settings, notably those by Talmor [18], Beitler [19], and Kassis [20]. Selected data from these studies are summarized in Table 1.

Two observations emerge consistently from these data.

First, the calculated compliance of the thoracic wall remains within a near-normal range.  $C_{TW}$  can be estimated from tidal volume ( $TV$ ) and the difference between end-inspiratory and end-expiratory  $P_{pl}$  ( $EIP_{pl}$  and  $EEP_{pl}$ , respectively):

$$C_{TW} \approx TV / (EIP_{pl} - EEP_{pl}) \quad (2)$$

Across the reported datasets, this yields values on the order of 120 ml.cmH<sub>2</sub>O<sup>-1</sup>, suggesting that the thoracic wall itself is not markedly stiff.

Second,  $EEP_{pl}$  is markedly elevated, typically around +15 to +18 cmH<sub>2</sub>O. If one assumes a normal reference  $P_{pl}$  of approximately -6 cmH<sub>2</sub>O at FRC, this implies an increase in thoracic volume of roughly:

$$\Delta V \approx (EEP_{pl} + 6) \times C_{TW} \quad (3)$$

which corresponds to an increase of several litres above FRC. Thus, the thorax appears to operate at substantially elevated volumes even at end-expiration.

These observations have important implications for airway patency. To maintain an alveolus open at such elevated  $P_{pl}$ ,  $P_{atv}$  must exceed  $P_{pl}$  by a sufficient margin. If one assumes that a pressure difference on the order of a few cmH<sub>2</sub>O ( $\approx 2-3$  cmH<sub>2</sub>O) is required to maintain airway patency, then  $P_{atv}$  in such regions must lie well above  $P_{pl}$ .

However, the  $P_{aw}$  available at end-expiration is limited by the applied PEEP. When the pressure required to keep peripheral units open exceeds this  $P_{aw}$ , those regions can no longer remain in communication with the airway tree and must therefore be functionally closed.

This reasoning suggests that, under the conditions reported in Table 1, a substantial fraction of the lung is likely to be excluded from ventilation at end-expiration. The concept of the “baby lung” [21] in ARDS is consistent with this interpretation: only a relatively small portion of the lung remains aerated and ventilated, while the remainder is functionally closed or fluid-filled.

An important consequence is that, during a low-flow inflation manoeuvre, the measured AOP may not be clearly discernible if PEEP is already close to or above the opening pressure of the least dependent lung regions. In that situation, the absence of a clearly defined AOP does not exclude substantial airway closure, because flow may begin immediately while a large part of the lung remains functionally closed.

Additional studies reporting elevated  $P_{pl}$  during mechanical ventilation, including observations in COVID-19 patients [22], support this overall picture of a lung compressed within a high-pressure thoracic environment. Under these conditions, airway closure, gas trapping, and redistribution of ventilation toward a limited “baby lung” appear as natural mechanical consequences [23] rather than isolated phenomena.

In addition, if expiratory flow limitation is present, incomplete emptying may further increase end-expiratory lung volume and  $P_{pl}$ , reinforcing airway closure and contributing to the characteristic combination of hyperinflation and a reduced “baby lung”.

**Table 1.** Pleural pressure ( $P_{es}$ ) measurements in mechanically ventilated ARDS patients. Data extracted from the studies of Talmor [18], Beitler [19] and Kassiss [20]. Cited variables are tidal volume,  $TV$ , End-Expiratory and End-Inspiratory pleural pressures,  $EEPpl$  and  $EIPpl$  and plateau pressure. The thorax wall compliance ( $C_{TW}$ ) and the extra volume above FRC (Extra V>FRC) were calculated from the provided data.

Author	Series	N	$TV$ (ml)	$EEPpl$ (mbar)	$EIPpl$ (mbar)	PEEP (mbar)	Plateau (mbar)	$C_{TW}$ (ml/mbar)	Extra V > FRC (ml)
Talmor	$P_{es}$ guided (base)	30	484	17.2	21.2	14.0	29	121	2807
	Conventional (base)	30	491	16.9	20.7	15.0	29	129	2959
	$P_{es}$ guided (72 h)	30	472	18.4	21.7	18.0	28	143	3490
	Conventional (72 h)	30	418	14.3	17.9	12.0	25	116	2357
Beitler	$P_{es}$ guided	102	396	16.0	19.0	14.0	28	132	2905
	Empirical PEEP	98	362	15.0	18.0	12.5	27	121	2531
Kassiss	Day 1	40	360	13.7	16.1	13.5	25	150	2955
	Day 3	38	390	13.0	15.9	13.0	24	134	2546

From a clinical perspective, it may be useful to consider whether the reduction in ventilated lung volume is predominantly driven by inflammatory consolidation or by pressure-dependent airway closure. Bed-side physiological markers such as the stress index and the recruitment-to-inflation (R/I) ratio may provide indirect insights into this distinction. The stress index, derived from the shape of the airway pressure-time curve during constant-flow inspiration, may suggest intratidal recruitment when compliance increases during inflation. The R/I ratio estimates the proportion of volume gain with higher PEEP that is attributable to recruitment rather than further inflation of already open units.

For example, a high recruitability, reflected by an elevated R/I ratio, may indicate that non-aerated regions can be reopened, whereas a low recruitability may be consistent with consolidated tissue or regions that remain closed due to persistent compressive forces. However, this distinction remains imperfect, as airway closure and inflammation frequently coexist and interact.

This underscores the importance of considering the mechanical environment, particularly pleural pressure, when interpreting the “baby lung” concept at the bedside.

## 8 Improvement by Reduction of Pleural Pressure

Experimental and clinical observations support the importance of  $P_{pl}$  in determining lung mechanics and injury. In a porcine model, Yoshida et al. [24] demonstrated that continuous negative abdominal pressure significantly reduced the severity of VILI. By lowering  $P_{pl}$ , this intervention reduced the compressive load on the lung and improved aeration of dependent regions.

More recently, Xiong and colleagues [25] applied negative pressure around the abdomen to limit and resolve postoperative atelectasis, further supporting the physiological rationale of external decompression of the thorax.

These findings are consistent with the broader physiological principle that reduction of  $P_{pl}$  facilitates airway patency and lung expansion. Interventions that decrease  $P_{it}$ —such as negative pressure applied externally or preservation of spontaneous inspiratory effort—tend to counteract airway closure and promote recruitment.

Spontaneous breathing during assisted ventilation illustrates this mechanism, as does Neurally Adjusted Ventilatory Assist [26]. Inspiratory muscle activity lowers  $P_{pl}$  and may partially offset the rise in  $P_{pl}$  induced by the ventilator. In this way, part of the required pressure is generated by the diaphragm rather than imposed via the airway, limiting increases in compressive load within the thorax.

Prone positioning provides a clinically well-established example of the beneficial effects of reducing  $P_{pl}$ . When applied correctly—i.e., with the abdomen allowed to hang freely—abdominal pressure on the diaphragm is reduced, permitting caudal displacement of the diaphragm

and lowering  $P_{pl}$ , particularly in dependent lung regions. This reduction in compressive load promotes more homogeneous ventilation and facilitates recruitment.

The physiological and clinical benefits of prone positioning in ARDS, including improved oxygenation and reduced mortality, have been demonstrated in the PROSEVA trial by Guérin et al. [27]. While these effects are commonly attributed to improved ventilation-perfusion matching and redistribution of lung densities, the associated reduction in  $P_{pl}$  may, at least in part, represent a key underlying mechanism contributing to the improved homogeneity of ventilation observed during prone positioning.

Together, these observations support the concept that reducing  $P_{pl}$  is not merely a theoretical consideration but a practical means of improving lung function and mitigating injury.

## 9 Absorption Atelectasis and Pulmonary Edema

Once a lung unit has become isolated by airway closure, gas absorption may convert functional exclusion into persistent atelectasis. Oxygen is gradually absorbed into the pulmonary capillary blood, reducing alveolar gas volume and lowering  $P_{abv}$ . If insufficient poorly soluble gas remains, the alveolus may collapse completely. This is the mechanism of absorption atelectasis emphasized by Hedenstierna [28] and others and explains why high inspired oxygen fractions may aggravate collapse in poorly ventilated lungs.

The subsequent fate of such a collapsing unit is governed not only by gas dynamics but also by fluid balance across the alveolo-capillary barrier. This balance is described by the Starling equation:

$$J = K[(P_1 - P_2) - \sigma(\pi_1 - \pi_2)] \quad (4)$$

where  $P$  denotes hydrostatic pressure,  $\pi$  oncotic pressure (largely determined by plasma proteins such as albumin),  $K$  the filtration coefficient, and  $\sigma$  the reflection coefficient.

Under normal conditions, hydrostatic and oncotic forces are balanced, resulting in minimal net fluid flux. However, a decrease in  $P_{abv}$  due to gas absorption alters the local hydrostatic gradient across the alveolar wall. This shift favours movement of fluid from the interstitium into the alveolar space.

As a result, the gas volume lost by absorption may be replaced by liquid, stabilizing the collapsed state. In this way, airway closure not only initiates atelectasis, but may also promote its persistence through fluid accumulation [29].

## 10 Implications for Ventilation Strategy

These considerations suggest that lung-protective ventilation should not focus exclusively on tidal volume reduction [30]. An equally important goal may be limitation of excessive  $P_{pl}$  and  $P_{it}$ .

PEEP should be interpreted as a compromise between airway stabilization and tissue compression. AOP should be used as an indicator of closure, but its absence not as proof of full reopening. Flow-controlled ventilation deserves attention because gradual pressure change may reduce peripheral exclusion.

Preservation of spontaneous inspiratory effort, when well synchronized with ventilator support, may also be beneficial because diaphragmatic activity can partly substitute for ventilator-generated pressure and thereby limit the rise in  $P_{pl}$ . By contrast, vigorous inspiratory effort against a closed system may generate very negative  $P_{alv}$ 's and promote edema.

Finally, NPV and related decompressive approaches merit renewed consideration. By lowering  $P_{pl}$  rather than raising  $P_{aw}$ , NPV expands the lung while reducing parenchymal compression and promoting peripheral airway patency. Historical observations, experimental data, and recent clinical applications of extra-thoracic or abdominal negative pressure all support the physiological rationale for revisiting this principle with modern monitoring techniques.

## 11 Conclusions

Airway closure during mechanical ventilation should not be regarded merely as an incidental or late phenomenon. It is a predictable mechanical consequence of elevated absolute pressure around the parenchyma, especially in dependent regions and in lungs with reduced compliance or increased chest wall load.

The distinction between  $P_{tp}$  and absolute  $P_{it}$  is therefore crucial. During PPV, the rise in  $P_{aw}$  is accompanied by a rise in  $P_{pl}$ , so that inflation occurs under conditions of increased parenchymal compression. This environment promotes peripheral airway closure, impaired recruitment, gas trapping, absorption atelectasis, and possibly pulmonary edema. In contrast, spontaneous breathing and NPV expand the lung while lowering the surrounding pressure.

Recognizing airway closure as a consequence of lung tissue compression may help reinterpret several familiar clinical phenomena, including AOP, PEEP responsiveness, delayed pneumothorax, hyperinflation, and the "baby lung". It also suggests that future lung-protective strategies should pay greater attention not only to volume, but to the absolute pressure environment within which that volume is delivered.

Importantly, airway closure should not be viewed solely as a pathological phenomenon. Under physiological conditions, it likely serves a protective role by limiting ventilation of regions where effective gas exchange is not beneficial and by preventing excessive local stress. The paradox arises when this inherently protective mechanism is exposed to an altered mechanical environment. During positive pressure ventilation, elevated intrathoracic pressure transforms airway closure from a regulated, adaptive process into a widespread and persistent phenomenon, contributing to gas trapping, impaired recruitment, and lung injury. In this context, what is normally protective becomes pathological.

## ABBREVIATIONS

The following abbreviations are used in this manuscript:

**ARDS** Adult Respiratory Distress Syndrome

**PEEP** Positive End Expiratory Pressure

**COPD** Chronic Obstructive Pulmonary Disease

**FRC** Functional Residual Capacity

**TV** Tidal Volume

**NPV** Negative Pressure Ventilation

**PPV** Positive Pressure Ventilation

**$P_{alv}$**  Alveolar pressure

**$P_{tp}$**  Transpulmonary pressure ( $= P_{alv} - P_{pl}$ ) opposite to  $P_L = P_{aw} - P_{pl}$

**$P_{aw}$**  Airway pressure

**$P_{pl}$**  Pleural pressure

**$P_{it}$**  Intrathoracic pressure  $= (P_{aw} + P_{pl})/2$

**$C_{lungs}$**  Compliance of the lungs

**$C_{TW}$**  Compliance of the thorax wall

**EEP<sub>pl</sub>** End-Expiratory pleural pressure

**EIP<sub>pl</sub>** End-Inspiratory pleural pressure

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