Alveolar mechanics: A new concept in respiratory monitoring

Ehab G. Daoud, [1] Claudio Luciano Franck [2]

DOI: https://doi.org/10.53097/JMV.10065

Cite: Daoud EG, Franck CL. Alveolar mechanics: A New Concept in Respiratory Monitoring. J Mech Vent 2022; 3(4):178-.188.

Abstract

A detailed understanding of respiratory mechanics during mechanical ventilation aids diagnostic accuracy and facilitates close monitoring of patient progress, allowing individualized ventilator adjustments aimed at minimizing ventilator induced lung injury. Respiratory mechanics can be described in terms of total respiratory, lung, and chest wall components and include compliance, resistance and are dependent on tidal volume, airway pressures, and flow for calculation. The interplay between the respiratory mechanics and ventilator delivered volume, flow, and pressure have an important role in the development of ventilator induced lung injury.

The knowledge of alveolar dynamics and mechanics in the critically ill are lacking with much information originating mainly from bench and animal models of healthy and injured lungs.

In this article we introduce the concept of alveolar compliance, resistance that depend on measuring the trans-alveolar pressure using esophageal balloon manometry and alveolar tidal volume using volumetric capnometry.

This may have multiple implications in the understanding of components of ventilator induced lung injury specifically alveolar stress, strain, and mechanical power.

Further studies are warranted to further understanding the monitoring and usefulness of alveolar mechanics.

Keywords: Alveolar compliance and resistance, alveolar tidal volume, trans-alveolar pressure, alveolar stress and strain, alveolar mechanical power

Authors
1. MD, FACP, FCCP. Professor of Medicine, JABSOM School of Medicine, University of Hawaii, USA.
2. MD, PhD. Faculdade Evangélica Mackenzie do Paraná, Hospital Universitário Evangélico Mackenzie, Brazil

Corresponding author: edaoud@hawaii.edu
Conflict of interest/Disclosures
Funding: None

Acknowledgment: Figures 1,2,6 illustration by Robert Cabbat RRT, Hawaii, USA.

Introduction

Understanding respiratory physiology and mechanics [1] during mechanical ventilation is crucial for monitoring patients and making ventilator adjustments to achieve individualized support without iatrogenic injury.

Respiratory mechanics refer to the expression of the respiratory system function through measurements of pressure and flow. From these, a variety of indices can be determined like tidal volume (V_T) and can be plotted against time or each other to obtain pressure-volume, pressure-flow, volume-flow curves. Inspiratory and expiratory pause maneuvers can further estimate the end inspiratory pressure (plateau pressure, P_{Plat}) and total positive end expiratory pressure (PEEP) respectively. [2,3]

Ventilator Induced Lung Injury (VILI) [4,5,6] with its many forms: volutrauma, barotrauma, atelectrauma, biotrauma, ergotrauma mostly happens due to injury at the alveolar level, emphasizing that knowledge of alveolar dynamics and mechanics requires better understanding and ventilation management needs to target those alveolar dynamics. [7]

Knowledge of alveolar dynamics and mechanics at the micro level originate from direct viewing and measurements of alveolar volumes, sizes, shapes, and interaction in healthy and injured animal lung models using different technologies. [8] Those include Intravital microscopy (IVM), Optical coherence tomography (OCT) and through the work of physiologists, we have a better understanding of alveolar expansion, contractility, stability, recruitment, and collapse during the respiratory cycle. [7] Those techniques, albeit their benefits, have some limitations including the need surgical procedures and limited depth in a regional part of the lung that hinders those techniques to only be applicable to research projects but not to the bedside in respiratory failure patients.

Currently, clinicians assess lung morphology, injury, aeration through information obtained from Computerized Tomography scans (CT) [9] and Electrical Impedance Tomography (EIT). [10] Although significant information can be obtained with those imaging techniques, they have many limitations including the macro level information supplied but not at the micro alveolar level.

Hence, an assessment of the alveolar mechanics non-invasively at the bedside would be elnllightening.

Alveolar pressures

The measurements of esophageal pressure (P_{es}) using an esophageal balloon manometry as a surrogate for pleural pressure ($P_{Pleural}$) provides further information about the lung, chest wall mechanics, muscle pressure (Pmus), work of breathing (WOB) among other benefits. [11]

The pressures obtained from the airway and esophageal pressures and during brief inspiratory and expiratory occlusions are [12]

Trans-Respiratory pressure (P_{TR})

Airway pressure (P_{AO}) – Body surface pressure (P_{BS})

Trans-Pulmonary pressure (P_{TP})

Airway pressure (P_{AO}) - Pleural pressure (P_{PL})

Trans-Alveolar pressure (P_{TA})

Alveolar pressure (P_A) - Pleural pressure (P_{PL})

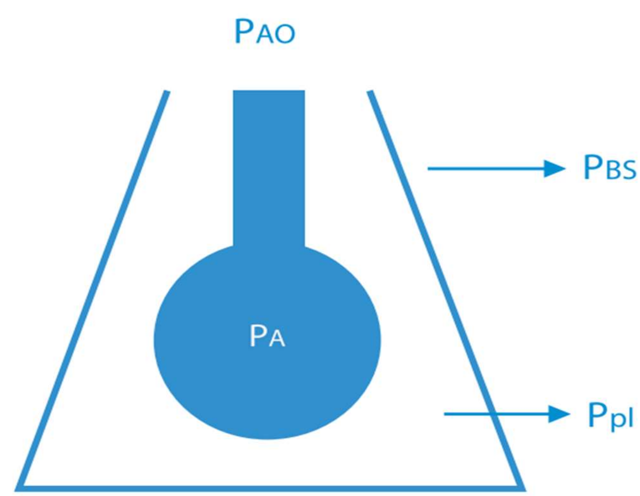

Figure 1: Schematic diagram of the chest wall and lung with the pressures across the structures. P_A: alveolar pressure, P_{AO}: airway pressure, P_{BS}: body surface (atmospheric) pressure, P_{PL}: pleural pressure.

The common mechanics that can be calculated during static (passive) and dynamic (active) conditions are the Compliance, Elastance (1/Compliance), Resistance, and total PEEP. Those can further be divided into: Total respiratory, Lung, Chest wall according to the calculations below [13]

Total respiratory compliance

V_T / DP
V_T / P_{plat} - $PEEP_T$

Total respiratory resistance

P_{PIP} - P_{plat} / $\dot{V}$

Chest wall compliance

V_T / End inspiratory P_{es} - End expiratory P_{es}

Chest wall resistance

Peak P_{es} - End inspiratory P_{es} / $\dot{V}$

Lung compliance

V_T / Trans-Pulmonary DP
V_T / End inspiratory P_{PL} - End expiratory P_{PL}

Lung resistance

Peak P_{PL} - End inspiratory P_{PL} / $\dot{V}$

Trans-alveolar DP = End inspiratory Tans-alveolar pressure – End expiratory Tans-alveolar pressure

Where DP: driving pressure, P_{aw}: airway pressure, P_{es}: esophageal pressure, PEEP: positive end expiratory pressure, P_{PIP}: peak inspiratory pressure, $P_{PL:}$ trans-pulmonary pressure, $\dot{V}$: flow, V_T: tidal volume

Alveolar Volume

The total tidal volume (V_T) delivered by the ventilator used for the measurements of the respiratory mechanics above can be further divided into dead space and alveolar V_T.

The total dead space (VD) represents the volume of ventilated air that does not participate in gas exchange. The two types of VD are anatomical (VD_{ana}) and physiologic (VD_{phys}). VD_{ana} is represented by the volume of air that fills the conducting zone made up by the artificial airway, trachea, and bronchi. VD_{phys} or total dead space is equal to anatomic plus alveolar dead space (VD_{alv}) which is the volume of air in the respiratory zone that does not take part in gas exchange. [14]

The alveolar V_T is composed of two compartments, the part that does not participate in gas exchange (VD_{alv}) and the effective part that partakes in gas exchange (V_{Ealv}). Figure 2

$$VD_{phys} = VD_{ana} + VD_{alv}$$

$$V_T = VD_{ana} + V_{Talv}$$

$$V_{Talv} = VD_{alv} + V_{Ealv}$$

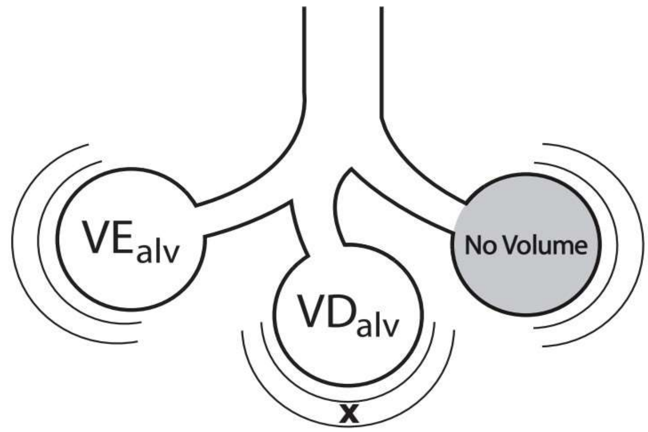

Figure 2: Schematic drawing showing 3 different alveoli with their corresponding capillaries. On the left: well perfused and ventilated alveolus with effective alveolar volume (VE_{alv}), the middle is a ventilated but not perfused alveolus and is considered as alveolar dead space (VD_{alv}), and the right one is an alveolus that is perfused but filled with fluid or collapsed (shunt).

In a healthy adult, VD_{alv} can be considered negligible. Therefore, VD_{phys} is considered equivalent to anatomical.[15] However, in the injured lung, especially in patients with ARDS, the VD_{phys} could be significantly high because the diffusion membrane of alveoli does not function properly or when there are ventilation/perfusion mismatch defects, [16,17] and has been correlated with mortality in ARDS. [18]

The V_D/V_T is calculated using the Enghoff modification of Bohr's equation

$$VD/V_T = (PaCO_2 - \bar{P}ECO_2) / PaCO_2$$

$PaCO_2$: partial pressure of CO_2 in arterial blood, $\bar{P}ECO_2$ expired partial pressure of CO_2.

The volumetric capnometry is divided into three phases. Phase I represents the VD_{ana}, Phase II represents the transition phase: gas from proximal lung areas and fast emptying lung areas, while Phase III is the plateau phase: gas from alveoli and slow emptying areas (Figure 3).

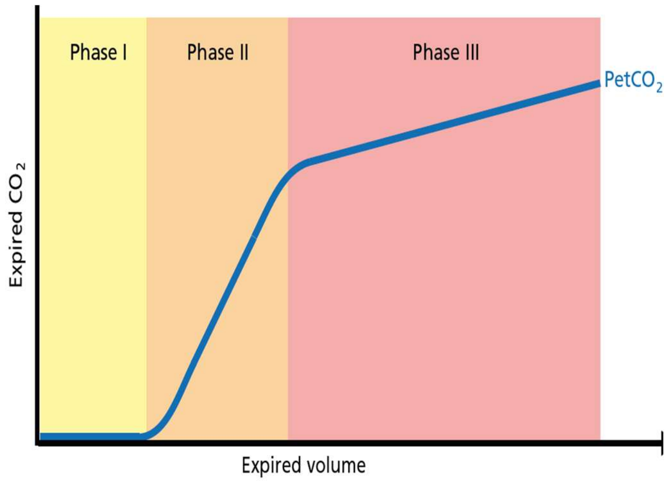

Figure 3: Three phases of the volumetric capnometry. (Hamilton Medical reference book) [19] with permission

Components of the exhaled V_T: physiological dead space (anatomical and alveolar dead space) and effective alveolar V_T can be calculated using volumetric capnometry as below. [8,20]
The anatomical dead space can be calculated from the curve of the V_T on the x-axis to the exhaled CO_2 on the y-axis by drawing a perpendicular line in the middle of phase II of the curve: area p + q (Figure 4).

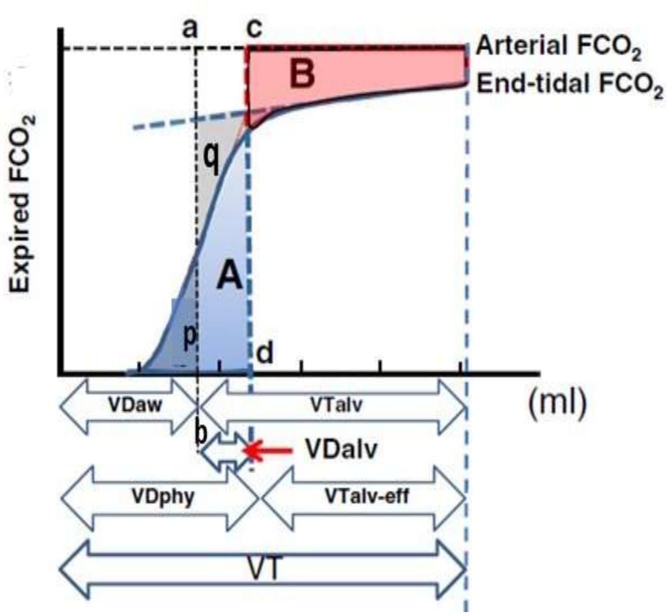

Figure 4: Estimation of dead space and alveolar tidal volume from the volumetric capnometry waveform. The black dashed line a–b defines equal area q and p in phase II. The volume to the left of this line represents the anatomical dead space, while the right of the line is the alveolar tidal volume. The blue dashed line c–d is created so that area A equals area B. The distance from b to d defines alveolar dead space. V_Daw: anatomical dead space, V_Talv: alveolar tidal volume, V_Dalv: alveolar dead space, V_Dphy: physiological dead space, V_Talv-eff (V_Ealv): effective alveolar volume, V_T: total tidal volume. From reference 20

Calculating Alveolar compliance and Resistance

As mentioned above, the V_T used in the equations of compliances is the total V_T including the anatomical V_T that is not involved in alveolar distention or gas exchange

Our hypothesis is to include only the total alveolar V_T

$$V_{alv} = VD_{alv} + VE_{alv}$$

and the trans-alveolar driving pressure (DP) as the true distending pressure of the alveoli [21] in the calculation of the true alveolar compliance.

Alveolar flow can be calculated by dividing alveolar tidal volume by the inspiratory time.

Alveolar resistance can be calculated as the trans-alveolar driving pressure (end inspiratory - end expiratory trans-alveolar pressure) divided by alveolar flow.

Alveolar compliance

$$V_T - VD_{anat} \text{ / Trans-alveolar DP}$$

$$V_{Talv} \text{ / Trans-alveolar DP}$$

Alveolar flow

$$\dot{V}_{alv} = V_{Talv}/T_{insp}$$

Alveolar resistance

$$R_{alv} = \text{Trans-Pulmonary pressure } (P_{PL}) - \text{Trans-Alveolar pressure } (P_{TA}) \text{ / } \dot{V}_{alv}$$

Deriving from the above formulas:

$$R_{alv} = (P_{PL} - P_{TA}) / (V_{Talv}/T_{insp})$$

$$R_{alv} = T_{insp} \text{ X } ((P_{PL} - P_{TA}) / V_{Talv})$$

In the example below (figure 5):

Alveolar compliance

= 214 / 10

= 21.4 ml/cmH_2O

Alveolar flow = 0.214 / 1.2

= 17.83 L/min

Alveolar resistance = 12 -11 / (17.83 / 60)

= 3.36 cmH_2O/L/s

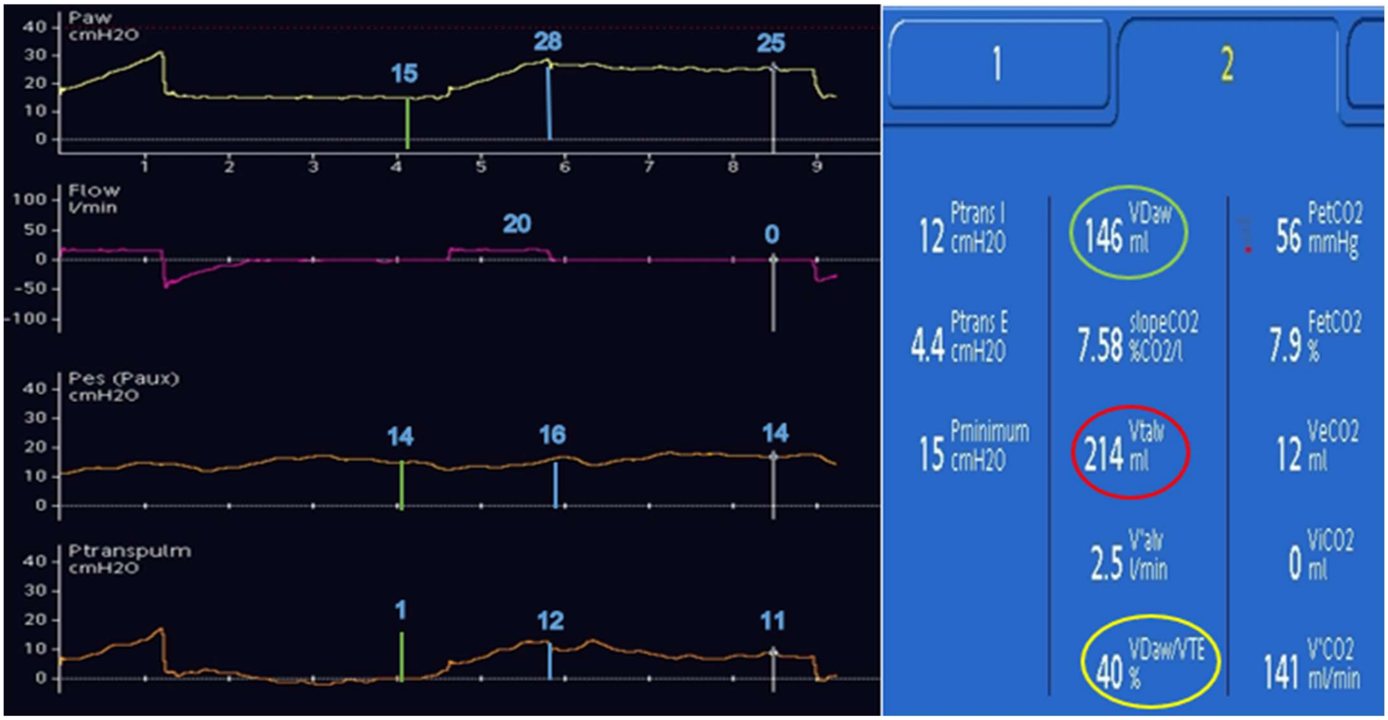

Figure 5 Left graph from a volume-controlled mode: Airway pressure (top in yellow) end expiratory airway pressure 15, peak inspiratory pressure 28, plateau inspiratory pressure 25. Flow (2nd row in pink): continuous flow of 20, end inspiratory and end expiratory flow of zero. Esophageal pressure (3rd row in orange): end expiratory pressure 14, peak inspiratory pressure 16, end inspiratory pressure 14. Airway pressure – Esophageal pressure (bottom row in orange) trans-pulmonary pressure of 12, end inspiratory trans-alveolar pressure 11, end expiratory trans-alveolar pressure 1. Right chart: V_{Daw}: anatomical dead space, V_{Talv}: alveolar dead space, Dead space/Tidal volume: V_{Daw}/V_{TE}
Pressures in cmH_2O, Flow in L/min, Volumes in ml

Discussion

Minimizing VILI is an important yet a difficult task during mechanical ventilation. Many factors have to be accounted for including V_T, DP, inspiratory flow, respiratory rate, respiratory mechanics and recently, mechanical power. Unfortunately, global lung mechanics provide for a poor surrogate of alveolar dynamics and methods for the in-depth analysis of alveolar dynamics on the level of individual alveoli are sparse and afflicted by important limitations. [7,8]

The exact mechanisms by how the alveolar gas moves in and out of the alveoli and alveolar ducts remains controversial and not totally understood, additionally healthy and injured alveoli act differently. [7,8]

There are two main mechanisms for gas flow into the lung, convection dependent (bulk gas flow or tidal flow) and a diffusion dependent. The two mechanisms can happen simultaneously and independently. [22] Volume change in healthy lungs occurs in the peripheral airways and diffusion occurs in the alveolar space. In the injured lung however, cyclic closure and reopening of alveoli can occur, and hence the convection-diffusion front has moved from the peripheral airways into the alveolar space. [23,24,25]

In an animal study, Gil and colleagues [26] introduced four different mechanisms of alveolar filling and emptying during the respiratory cycle: (1) sequential recruitment–decruitment of alveoli, (2) isotropic “balloon-like” alveolar volume change, (3) simultaneous changes in alveolar size and shape, and (4) crumpling and decrumpling of the alveolar surface. Another animal study of injured lungs by Mertens and colleagues [27] found out that alveolar cycling was not observed according to the concept of alveolar stability. [28]

Additionally, alveolar volume moves between alveoli through the Pendelluft phenomenon [29] and through the pores of Kohn, [30] with a role played by the alveolar septa in the stochastic movement of the molecular diffusion. [22]

The air movement in and out the alveoli during the respiratory cycle is dependent on the alveolar pressure and radius according to Laplace's law

$$\text{Pressure} = 2 \text{ X surface tension / radius}$$

The alveolar flow and resistance are much less than the bigger conducting airways like bronchi given the much larger alveolar surface area. [31]

To our knowledge, the concept of calculating the alveolar compliance and resistance at the bedside has not been described before.

Implications

- Alveolar strain

The tidal energy is a product of Stress (which is the pressure applied to the alveoli or trans-alveolar pressure) by Strain (which corresponds to the stretching alveolar tidal volume). [32]

The possibility of specifying the volumetric compartments from the volumetric capnography and thus obtaining the alveolar V_T separately from the anatomical VD conceptually should be more accurate in denoting the alveolar strain and consequently may correlate with its structural injuries.

- Alveolar stress

Strain describes the resulting change in lung volume by the applied pressure (stress). [33] A simplified equation for strain is [34]

$$V_T + V_{PEEP} / FRC$$

$$FRC = EELV \text{ measured at zero PEEP (ZEEP)}$$

where V_T = tidal volume; V_{PEEP} = difference between end expiratory lung volume (EELV) and Functional residual capacity (FRC).

Measurement of FRC during mechanical ventilation through nitrogen washout [35] is feasible but is not routinely available on all commercial ventilators.

As in most calculations of respiratory mechanics, the V_T used in the equations is the global V_T, our hypothesis is that the alveolar V_T may be a more reliable alternative in assessing the alveolar stress.

- **Guiding Tidal volume and PEEP**

Setting V_T and PEEP are essential during mechanical ventilation and guidelines exist in setting those parameters. [36] However, those guidelines do not take account of the VD and alveolar V_T and how those V_Ts and pressures affect the alveolar compliance.

Some studies addressing this issue using the VD measurements from volumetric capnometry to set the PEEP have been published. Blankman and colleagues found that the calculated VD agreed well with EIT to detect the optimal PEEP for an equal distribution of inspired volume, amongst non-dependent and dependent lung regions. [37] Tusman and colleagues evaluated the airway and alveolar VD in different PEEP settings in an animal model of ARDS. [38]

Technologic advances have been made to address these concerns. Adaptive Ventilation Mode-2 (AVM-2) is a closed loop mode of ventilation with an optimal targeting scheme using the concept of mean inspiratory power (sum of the resistive and tidal power) that takes the VD into account in its algorithm for targeting the optimal V_T and respiratory rate. [39,40]

- Alveolar resistance

As the above, we were able to describe the alveolar resistance which is not well described in the literature. The total pulmonary resistance is composed of the airway resistance, which may be responsible for as much as 80% of the total pulmonary resistance in a normal lung, is influenced by the velocity and pattern of airflow, geometry of the airways, and the density and viscosity of the gas itself. The tissue frictional resistance normally accounts for about 20% of the pulmonary resistance and is influenced by the configuration of the chest wall and the lung as well as by the fluid content of the pulmonary tissue. Inertial resistance that is less than 1% of pulmonary resistance is usually more dependent on the breathing frequency and the density of the gas. [41]

There are variations in the strain of a given V_T related to the ventilation mode and the inspiratory flow pattern, [42] however we used the basic formula of alveolar flow dividing the tidal alveolar volume by the inspiratory time, because the hypothesis that the pressure, the V_T and alveolar flow are the result of macroflow distribution in the alveolar elastance, which along each flow moment along the inspiratory time determines its V_T and produces its strain.

The total respiratory resistance is usually measured using the rapid interruption technique during constant flow volume control ventilation (inspiratory hold maneuver) where the initial drop of pressure from peak inspiratory to P1 represent the artificial and large airways resistance, while after a prolonged hold of 3-5 seconds, the pressure drops furthermore to P2 which represent the viscoelastic resistance P2 represent the plateau pressure that is equivalent to the alveolar pressure). [43] (Figure 6)

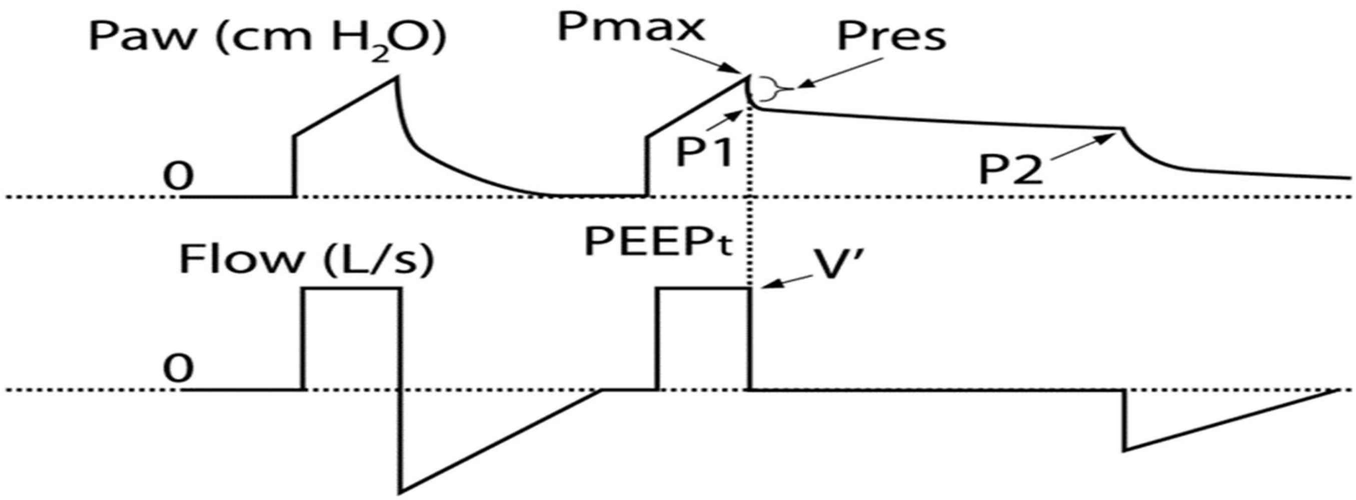

Figure 6: Airway pressure-time curve (top) and flow-time curve (bottom) in volume-controlled mode with constant inspiratory flow using an inspiratory holding maneuver. Pmax: peak inspiratory pressure, Pres: is the airway resistance (Pmax – P1), P1: is the initial drop of pressure at the beginning of the hold maneuver, P2: is the true plateau pressure at the end of the maneuver.

- Trans-alveolar pressure and Trans-alveolar mechanical power (MP)

The terms trans-pulmonary pressure and trans-alveolar pressure are sometimes used interchangeably (Figure 1)

Trans-pulmonary pressure (P_{TP}) is defined as: Airway pressure (P_{AO}) - Pleural pressure (P_{PL})

Trans-Alveolar pressure (P_{TA}) is defined as: Alveolar pressure (P_A) - Pleural pressure (P_{PL})

Thus, the true alveolar compliance as described above is the V_{Talv} / Δ P_{TA}

Using our described formula above, alveolar elastance = 1/compliance, we are able to calculate the trans-alveolar mechanical power.

Mechanical power (MP) is the amount of energy transferred from the ventilator to the respiratory system per unit time and has emerged as a new concept in the development of VILI [44] and mortality, [45] other studies [46] showed that the trans-pulmonary MP might be more related to mortality rather than the total power. Theoretically, the trans-alveolar MP may perform better than the total power, however, this needs to be investigated in clinical trials.

The total MP is described as [47]

$\mathbf{MP_{RS}}$ = (0.098 X RR) X {VT2 X ½ E_{RS} + (V_T X PEEP)}

The lung (trans-pulmonary) MP is described as [48]

$\mathbf{MP_{PL}}$ = (0.098 x RR) x {2 V_T x ½ E_L + (V_T x PEEP)}

The alveolar (trans-alveolar) MP similarly will be described as

$\mathbf{MP_{\mathit{Alv}}}$ = (0.098 X RR) x {2 V_{TAlv} x ½ E_{Alv} + (V_{TAlv} x PEEP)}

In the example in figure 5:

$\mathbf{MP_{RS}}$ = (0.098 x 15) x {0.72 X ½ (28) + (0.36 X 15)}

= 22.75 J/min

$\mathbf{MP_{PL}}$ = (0.098 x 15) x {0.72 X ½ (25) + (0.36 X 15)}

= 21.17

$\mathbf{MP_{Alv}}$ = (0.098 x 15) x {0.428 X ½ (42) + (0.214 X 15)}

= 17.92 J/min

Limitations

- The need for both esophageal balloon and volumetric capnometry

Our calculations are based on having two adjunctive tools to mechanical ventilation: esophageal balloon manometry and volumetric capnometry. The esophageal balloon estimates the pleural pressure and enables the calculation for the trans-alveolar pressure. Despite its' multiple benefits, [49] its use in clinical practice is influenced by technical limitations and lack of knowledge in application and remains more of a research tool. [50] Similarly, volumetric capnometry offers multiple important clinical information compared to only end tidal CO_2 monitoring. [51] Though its clinical use in practice is not documented, practice guidelines from 2011 [52] only suggested the use of volumetric capnometry to monitor patients during mechanical ventilation.

- Alveolar heterogeneity

The alveolar sizes, distribution and vascular distribution are markedly heterogeneous in both healthy [27] and injured lungs [53] and are influenced by the region of the lung zone and pleural pressure. Alveolar mechanics and time constant will vary depending on the position of alveoli and the disease process. Our formula, similar to all other respiratory mechanics formulas describe a global rather than regional mechanics. Despite this limitation, we believe that it gives additional information on the micro alveolar dynamics versus the total respiratory mechanics which describe the macro structure of the whole respiratory system.

Future directions

- Constructing trans-alveolar pressure – alveolar volume curve

Many current ventilators allow the construction of a low flow quasi static pressure-volume curve [54] to assess the respiratory system compliance. Some of those ventilators are also equipped with an esophageal balloon manometry and can plot the trans-pulmonary and trans-alveolar pressure -volume curve that assesses the respiratory system, lung and chest wall compliance. Though most of those ventilators are also equipped with volumetric capnometry, to our knowledge, none plot the trans-alveolar pressure-alveolar volume curve.

Figure 6 below, shows a quasi-static transpulmonary pressure – volume (P-V curve) curve in a patient with ARDS with IBW 65 kg, on V_T of 400 ml and measured anatomical dead space volume was 150 ml. Assuming the anatomical dead space does not change during the maneuver, we adjusted the volume (in red) by subtracting 150 ml from the total V_T (black). This has never been studied and needs further evaluation.

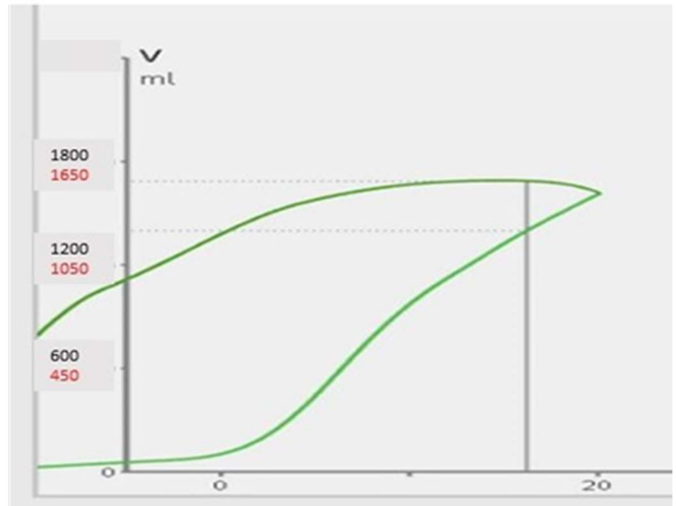

Figure 6: P-V curve plotting the trans-alveolar pressure vs the volume in a slow inflation quasistatic condition. Black numbers on the y-axis are the measured ones, while the red ones are the actual numbers – anatomical dead space (Alveolar tidal volume)

- Modeling respiratory mechanics

Most models of respiratory mechanics use a single compartment linear model with single resistance, and compliance which is over simplistic of the real heterogeneous respiratory system with millions of alveolar sacs each with their own mechanics and interdependent on other sacs and under different strain from inside alveolar pressure (P_A) and outside from different pleural pressures (P_{PL}). Even in clinical practice at the bedside, measurements are taken of total respiratory, lung, chest wall mechanics assuming a single compartment model similar to figure 1. As discussed above, the same problem confounds our concept. Recent sophisticated micromechanical lung models have been developed for better understanding and studying the human respiratory system. [19,55]

- Studying alveolar mechanics at the bedside

As described above, viewing the alveolar dynamics have been limited to research animal studies, and our current imaging technologies does not penetrate to the alveolar level. With the rapid advance in technology, it might be possible to non-invasively evaluate regional alveolar dynamics and the effects of mechanical ventilation on regional lung units.

Conclusion

An enhanced knowledge of the alveolar mechanics may add to clinicians understanding of the respiratory mechanics and alveolar injury. Clinical investigations to provide human data on alveolar mechanics, mechanical power and their effect on VILI and mortality are needed to verify our concept.

References

1. Henderson WR, Sheel AW. Pulmonary mechanics during mechanical ventilation. Respir Physiol Neurobiol 2012; 180(2-3):162-172.

2. Gertler R. Respiratory Mechanics. Anesthesiol Clin 2021; 39(3):415-440.

3. Daoud EG, Shimabukuro R. Mechanical ventilation for the non-critical care trained practitioner. Part 1. J Mech Vent 2020; 1(2):39-51.

4. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013; 369:2126–2136.

5. Uhlig S. Ventilation-induced lung injury and mechano transduction: stretching it too far? Am J Phys Lung Cell Mol Phys 2002; 282:L892–L896.

6. Marini JJ. Dissipation of energy during the respiratory cycle: conditional importance of ergotrauma to structural lung damage. Curr Opin Crit Care 2018; 24:16–22.

7. Carney D, DiRocco J, Nieman G. Dynamic alveolar mechanics and ventilator-induced lung injury. Crit Care Med 2005; 33(3 Suppl):S122-128.

8. Grune J, Tabuchi A, Kuebler WM. Alveolar dynamics during mechanical ventilation in the healthy and injured lung. Intensive Care Med Exp 2019; 7(Suppl 1):34.

9. Gattinoni L, Caironi P, Pelosi P, et al. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 2001; 164:1701–1711.

10. Simonpietri M, Shokry M, Daoud EG. Electrical Impedance Tomography: the future of mechanical ventilation? J Mech Vent 2021; 2(2):64-70.

11. Akoumianaki E, Maggiore SM, Valenza F. The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 2014; 189(5):520-531.

12. Chatburn RL, Daoud EG. Ventilation in Kacmarek, Robert M. et al. Egan's Fundamentals of Respiratory Care. Ed. Robert M. Kacmarek et al. Eleventh edition. St. Louis, Missouri: Elsevier, 2017.

13. Shokry M, Yamasaki K, Daoud EG. Can you calculate the total respiratory, lung, and chest wall respiratory mechanics? J Mech Vent 2020; 1(1):24-25.

14. Robertson HT. Dead space: the physiology of wasted ventilation. Eur Respir J 2015; 45(6):1704-1716.

15. Quinn M, St Lucia K, Rizzo A. Anatomy, Anatomic Dead Space. [Updated 2022 Feb 2]. In: StatPearls [Internet]. Treasure Island (FL): Available from: https://www.ncbi.nlm.nih.gov/books/NBK442016/

16. López-Aguilar J, Magrans R, Blanch L. Dead space in ARDS: Die hard. Respir Care 2017; 62(10):1372-1374.

17. Ferluga M, Lucangelo U, Blanch L. Dead space in acute respiratory distress syndrome. Ann Transl Med 2018; 6(19):388.

18. Murias G, Blanch L, Lucangelo U. The physiology of ventilation. Respir Care 2014; 59(11):1795–1807.

19. Voumetric capnometry. https: https://www.hamilton-medical.com/en_US/Landing-pages/Volumetric-capnography-ebook.html? Accessed October 2022

20. Verscheure S, Massion PB, Verschuren F, et al. Volumetric capnography: lessons from the past and current clinical applications. Crit Care 2016; 20:184.

21. Williams EC, Motta-Ribeiro GC, Vidal Melo MF. Driving pressure and transpulmonary pressure: how do we guide safe mechanical ventilation? Anesthesiology 2019; 131(1):155-163.

22. Paiva M. Gas transport in the human lung. Journal of Applied Physiology 1973; 35 (3):401-410
.
23. Schibler A, van der Staay M, Remus C. From state-of-the-art ventilation to closed loop ventilation J Mech Vent 2022; 3(3):92-104.

24. Paiva M, Verbanck S, van Muylem A. Diffusion-dependent contribution to the slope of the alveolar plateau. Respiration Physiology 1988; 72:257-270.

25. Verbanck S, Paiva M. Model simulations of gas mixing and ventilation distribution in the human lung. Journal of Applied Physiology 1990; 69:2269-2679.

26. Gil J, Bachofen H, Gehr P, et al. Alveolar volume-surface area relation in air- and saline-filled lungs fixed by vascular perfusion. J Appl Physiol Respir Environ Exerc Physiol 1979; 47:990–1001.

27. Mertens M, Tabuchi A, Meissner S et al Alveolar dynamics in acute lung injury: heterogeneous distension rather than cyclic opening and collapse. Crit Care Med 2009; 37:2604–2611.

28. Clements JA, Hustead RF, Johnson RF, et al. Pulmonary surface tension and alveolar stability. J Appl Physiol 1961; 16(3):444-450.

29. Enokidani Y, Uchiyama A, Yoshida T, et al. Effects of ventilatory settings on pendelluft phenomenon during mechanical ventilation. Respir Care 2021; 66(1):1-10.

30. Parra SC, Gaddy LR, Takaro T. Ultrastructural studies of canine interalveolar pores (of Kohn). Lab Invest 1978; 38(1):8-13.

31. Introduction to pulmonary structure & mechanics. In: Barrett KE, Barman SM, Boitano S, Reckelhoff JF. eds. Ganong's Medical Physiology Examination & Board Review. McGraw Hill; 2017.

32. Rocco PRM, Silva PL, Samary CS, et al. Elastic power but not driving power is the key promoter of ventilator-induced lung injury in experimental acute respiratory distress syndrome. Crit Care 2020; 24(284):1-8.

33. Hubmayr RD, Kallet RH. Understanding pulmonary stress-strain relationships in severe ARDS and its implications for designing a safer approach to setting the ventilator. Respir Care 2018; 63(2):219-226.

34. Blankman P, Hasan D, Bikker IG, Gommers D. Lung stress and strain calculations in mechanically ventilated patients in the intensive care unit. Acta Anaesthesiol Scand 2016; 60(1):69-78.

35. Brewer LM, Orr JA, Sherman MR, et al. Measurement of functional residual capacity by modified multiple breath nitrogen washout for spontaneously breathing and mechanically ventilated patients. Br J Anaesth 2011; 107(5):796-805.

36. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care 2019; 13;9(1):69.

37. Blankman P, Shono A, Hermans BJ, et al. Detection of optimal PEEP for equal distribution of tidal volume by volumetric capnography and electrical impedance tomography during decreasing levels of PEEP in post cardiac-surgery patients. Br J Anaesth 2016; 116(6):862-869.

38. Tusman G, Gogniat E, Madorno M, et al. Effect of PEEP on dead space in an experimental model of ARDS. Respir Care 2020; 65(1):11-20.

39. Yeo J, Shah P, Koichi K, et al. Mechanical power in AVM-2 versus conventional ventilation modes in in various ARDS lung models: A bench study. J Mech Vent 2022; 3(3):110-122.

40. Schibler A, van der Staay M, Remus C. From state-of-the-art ventilation to closed loop ventilation J Mech Vent 2022; 3(3):92-104.
41. Abbasi S, Sivieri EM, Bhutani VK. Evaluation of pulmonary function in the neonate, fetal and

neonatal physiology (Third Edition), Saunders WB2004 (90): 919-926.

42. Crooke PS, Gattinoni L, Michalik M, et al. Intracycle power distribution in a heterogeneous multi-compartmental mathematical model: possible links to strain and VILI. Intensive Care Med Exp 2022; 10(1):21.

43. Guerin C, Richard JC. Measurement of respiratory system resistance during mechanical ventilation. Intensive Care Med 2007; 33:1046–1049.

44. Paudel R, Trinkle CA, Waters CM, et al. Mechanical power: A New concept in mechanical ventilation. Am J Med Sci 2021; 362(6):537-545.

45. Tonna JE, Peltan I, Brown SM, et al. University of Utah Mechanical Power Study Group. Mechanical power and driving pressure as predictors of mortality among patients with ARDS. Intensive Care Med 2020; 46(10):1941-1943.

46. Coppola S, Caccioppola A, Froio S, et al. Effect of mechanical power on intensive care mortality in ARDS patients. Crit Care 2020; 24(1):246.

47. Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016; 42(10):1567-1575.

48. Arnal JM, Saoli M, Garnero A. Airway and transpulmonary driving pressures and mechanical powers selected by INTELLiVENT-ASV in passive, mechanically ventilated ICU patients. Heart Lung 2020; 49(4):427-434.

49. Pham T, Telias I, Beitler JR. Esophageal manometry. Respir Care 2020; 65(6):772-792.

50. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with Acute Respiratory Distress Syndrome in intensive care units in 50 countries. JAMA 2016; 315(8):788-800.

51. Kreit JW. Volume capnography in the intensive care unit: potential clinical applications. Ann Am Thorac Soc 2019; 16(4):409-420.

52. Walsh BK, Crotwell DN, Restrepo RD. Capnography/Capnometry during mechanical ventilation: 2011. Respir Care 2011; 56(4):503-509.

53. Hurtado DE, Erranz B, Lillo F, et al. Progression of regional lung strain and heterogeneity in lung injury: assessing the evolution under spontaneous breathing and mechanical ventilation. Ann. Intensive Care 2020; 10:107.

54. Harris RS. Pressure-volume curves of the respiratory system. Respir Care 2005; 50(1):78-98.

55. Concha F, Sarabia-Vallejos M, Hurtado DE. Micromechanical model of lung parenchyma hyperelasticity, Journal of the Mechanics and Physics of Solids 2018; 112:126-144.