Respiratory Monitoring

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Overview

Introduction

Respiratory failure, both acute (ARF) and chronic, is a life threatening global challenge. It is a dynamic complex syndrome originating from diverse pathologies; acute respiratory distress syndrome (ARDS), affecting a quarter of ventilated patients, being the most challenging. As unguided interventions were shown to add insult to the original injury, diagnosis and close monitoring are warranted. While remote community monitoring is growing, this chapter will focus on bedside respiratory monitoring in the acute settings.

Clinicians aim to treat acute respiratory failure (ARF) with minimal therapy associated harm. While society guidelines and lung protective strategies provide a framework of parameters, targets, and limits, their application to individual patients can yield variable outcomes. The heterogeneity of patient specific factors including host response, underlying pathology, and disease severity renders a unified approach less effective. Additionally, respiration involves a dynamic interplay of multiple physiological mechanisms and organ systems. Clinicians must diagnose the underlying cause, monitor deterioration to enable timely intervention, provide safe respiratory support when necessary, assess for improvements and readiness to wean the support. Throughout this process, an individualized approach is increasingly advocated, necessitating an effective and comprehensive monitoring strategy.

Monitoring as integral to respiratory support

Acute respiratory support (RS) is used as a bridge for recovery or long term support. It can take place anywhere from pre-hospital to the intensive care units (ICUs) and includes conventional oxygen, high flow nasal oxygen (HFNO), mechanical ventilation (MV) and extracorporeal support. The application is not uniform worldwide, including doctors, nurses or respiratory therapists with variable degrees of competencies, especially out of hours.

The aim of RS is to improve the gas exchange and work of breathing while keeping to a minimum the harms arising from the support itself (e.g., dyssynchronies, lung and diaphragmatic injury). A complex decision making is needed in the more complex cases and the role of monitoring here is to support decisions to be precise, accurate, safe and timely.

In the ICU, precision is mostly physiologically based. Respiration involves the constant interplay of many organs (e.g., brain, heart, lungs, muscles, etc.) (Fig 1). Effective monitoring will capture, record, integrate, simplify and display such complexity and dynamism for every single patient. One step further is the move by the industry to integrate all monitored data into a single platform and furthermore use machine learning

and artificial intelligence to create autonomous ventilator adjustments in a closed loop fashion. Nevertheless, this remains currently premature, and its blind application is not without risks.

Principles of Monitoring

Monitoring can be basic or advanced, intermittent or continuous. Targeting the gas exchange at its end point (e.g., blood or tissue oxygenation) is common but overlooks the underlying pathophysiology. In many cases, the therapy itself can influence many elements simultaneously, whether in a positive or a negative way. Identifying the underlying derangement(s), whether the respiratory drive, neuromuscular system, airways, lungs and chest wall mechanics, is the goal of advanced monitoring.

Monitoring can be clinical or requires sophisticated equipment. Mechanical ventilators themselves are increasingly serving as monitors but with some limits. An ideal monitor will provide a bedside, real time, continuous, accurate, inexpensive, simple to interpret, free from noise signals. Monitoring per se is not expected to improve the outcome, while the correct timely action by the operator can. As such, without a proper understanding and application, an expensive equipment can become useless or even harmful.

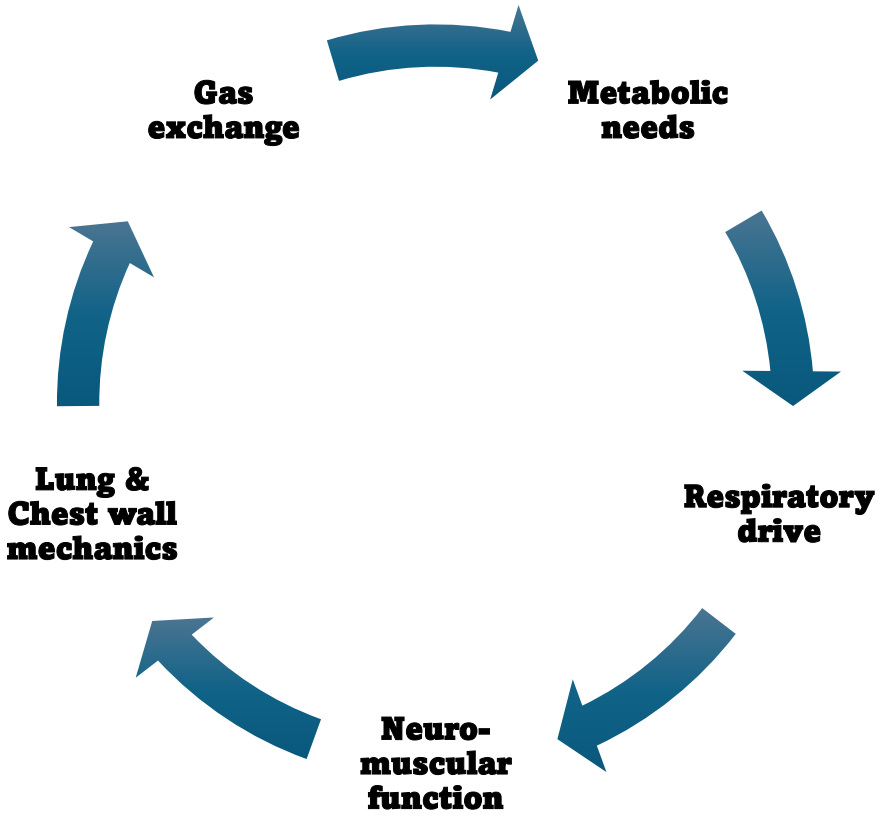


Figure 1: The different targets of respiratory monitoring

Respiratory monitored parameters

Clinical respiratory monitoring

1. Respiratory drive

The respiratory drive refers to the intensity of the respiratory centers output (RCO) which mainly controls the ventilation (CO_2 elimination). RCO is then translated into an inspiratory flow-generation pathway through a neural pathway and the respiratory muscles. A depressed drive will lead to respiratory failure, while an increased one can lead to ventilator induced lung injury (VILI), self-inflicted lung injury (SILI) and ventilator induced diaphragmatic dysfunction (VIDD). Nevertheless, it is impossible to directly measure the respiratory drive, and it is usually assessed through its mechanical output (breathing effort).

The central control of breathing resides in the brain stem and cerebral cortex. The central control is connected to a control arm (flow-generation neuromuscular pathway) and feedback sensory mechanisms. Carbon dioxide is the strongest stimulus of the respiratory centers, however, the slope of the response can be affected by hypoxia, the acid base status, sleep and sedation.
During critical illness, it is possible that the RCO to be discrepant from the actual Minute Ventilation (V_{min}) if the control arm is dysfunctional or the lung mechanics are deranged. Vaporidi et al suggested a brain curve and ventilation curve to illustrate such discrepancy. The 2 curves are identical in physiological states, but when the ventilation curve shifts downward and to the right this leads to equilibrium at higher $PaCO_2$ levels. This discrepancy can be due to the respiratory center/brain curve (e.g., hyperoxemia, metabolic alkalosis, sleep and sedation) or inspiratory flow-generation pathway dysfunction (i.e., ventilation curve). To note that the respiratory drive can also recruit the expiratory muscles during respiratory distress. Apart from respiratory failure, assessing the respiratory drive is essential also during weaning from mechanical ventilation.

As mentioned above, the respiratory drive cannot be estimated directly, either the $P_{0.1}$ or the breathing effort (neuromuscular function) are used as a surrogate (see later).

2. Respiratory rate (RR)

Patients recruit their respiratory reserve either by increasing the inspired volume (tidal volume) or by increasing the respiratory rate (RR).

RR is one of the four vital signs and a cornerstone of the early warning scores. Concomitant pathology (e.g., sepsis, acute neurological injury) and drugs (e.g., opiates) can interfere with the respiratory centers and lead to inappropriately increased or reduced RR. Despite such caveats, RR can precede changes in other early warning components and its extreme values are associated with mortality.
In critically ill patients, the unstressed RR was found to be higher than normal adults by about 10 cycles/min. This is true also in patients with brain injury when they lose the cortical inhibitory effect exerted on the respiratory centers.

RR can be simply counted or watched on bedside monitors. More importantly, it is to recognize the underlying cause (whether respiratory decompensation or other causes), but unfortunately it was shown that clinicians are less mindful of the RR significance. The increase in spontaneous RR in respiratory failure most often follows the increase in muscular effort, so considered a sign of fatigue and decompensation which deserves prompt action.

In mechanically ventilated patients, the RR is set by the operator in controlled modes or triggered by the patient in assisted and spontaneous modes. Displayed RR might be different than the intrinsic patient's trigger. Ineffective efforts and false triggering are examples. Tachypnea can be a sign of under assistance. While the harm of pressure and volume are much appreciated by physicians, the contribution of a high RR (and flow) are generally less appreciated (see mechanical power). This includes hyperinflation (intrinsic PEEP) due to inadequate expiratory time, increase in the right ventricular afterload, and multiplying the times an injurious breath and energy are applied to the lungs (mechanical power).

3. Respiratory pattern and accessory muscle use

In response to an increased respiratory drive, more forceful contraction of the muscles is needed to increase the inspired volume. The main muscle is the diaphragm, but there might be a need to recruit more muscles (accessory muscles). The excessive use of accessory muscles and expiratory muscles is a sign of deterioration. By increasing lung strain and stress, such excessive effort can lead to patient SILI and myotrauma.

Lung Volumes Monitoring

Pulmonary Function Test (PFT)

(Will be covered in detail in separate chapter)

In spontaneous breathing patients, Pulmonary function tests (PFTs) are crucial diagnostic tools used to assess the functionality of the respiratory system. These tests encompass a variety of measurements that evaluate how well the lungs take in and release air, and how efficiently they exchange gases and pulmonary impairment. PFT has diagnostic and therapeutic roles. Key parameters such as lung volume, capacity, airflow, and gas exchange efficiency are assessed through PFTs. Analyzing these metrics, aid in diagnose and monitor conditions like obstructive and restrictive lung diseases. PFTs play a pivotal role in guiding treatment decisions and tracking the progression of respiratory diseases.

Tidal volume (VT)

During mechanical ventilation, Tidal volume (VT) is readily displayed on the invasive and non-invasive ventilators' screens. However, tidal volumes are not directly measured by the ventilator but integrated from the flow which is directly measured (VT = Flow x Time) usually the expiratory one (VTe). The difference between the inspiratory and expiratory tidal volume reflects the leak and sometimes the ventilator tubing compliance.

Since the ARMA trial, a VT of 4-8 ml/kg PBW (predicted body weight) was recommended in invasive MV in ARDS. VT causes lung expansion (deformation) which represent the lung strain when correlated to the baseline size (EELV or functional residual capacity, FRC). Even a slightly elevated VT can lead to volutrauma in the less aerated derecruited lungs (baby lungs). VT is difficult to control during non-invasive ventilation (NIV), and a value > 9.5 ml/Kg PBW can predict NIV failure in hypoxemic respiratory failure.

Gas Exchange Monitoring

The main function of the respiratory system is to secure an adequate gas exchange (i.e., provide adequate oxygen and eliminate carbon dioxide) to fulfil the metabolic needs. While lungs oxygenate blood passing through, carrying and extracting oxygen at tissue level requires adequate circulatory and cellular functions. As such, respiratory monitoring should not be a standalone approach when facing multi-organ dysfunction.

1. Pulse oximetry

Different hemoglobin (Hb) types absorb light at different wavelength. Pulse oximeters translate such phenomenon into a percentage of oxygen saturation, SpO_2 (OxyHb/total Hb). It captures also the pulse rate based on plethysmography, which when visually displayed reflects the quality of the signal and hence accuracy of the reading. Oximeters are widely used due to their simplicity and low cost and can be placed on the fingers, toes, forehead, nose or ears. Home oximeters are available, but with variable accuracies.

Skin color, perfusion, temperature and motion can impede the signal and lead to false results. There is a weak correlation with partial arterial oxygen tension (PaO_2) at extreme values (e.g., SpO_2 <80% or 100%). The presence of abnormal Hb (e.g., Carboxyhemoglobin and Methemoglobin) can lead to false readings. To note that the numerical target of SpO_2 was recently revisited in many trials and best to be personalized with growing emphasis on the harm of hyperoxemia.

The SpO_2/FiO_2 ratio was suggested as a surrogate of the classic PaO_2/FiO_2. This is of particular interest in resource limited settings or in out of ICU settings where less staffing is available and arterial lines not in use. The new global definition of ARDS supported using SpO_2/FiO_2 ratio ≤ 315 for diagnosis (equivalent to PaO_2/FiO_2 <300). In such way, SpO_2/FiO_2 can more rapidly and accurately detect and classify ARDS (SpO_2/FiO_2 thresholds: mild 234-314; moderate 148-235, or severe ARDS ≤ 148). Nevertheless, pulse oximeters are late detectors of hypoventilation (type 2 respiratory failure) and cannot stand alone as a respiratory monitor.

Lastly, monitoring the combination of RR and SpO_2 can predict the failure of HFNO. This can be achieved by using the ROX index:

$$\textbf{ROX Index} = (SpO_2/FiO_2)/\ RR$$

A lower value denotes more probability of HFNO failure, and a value greater than 4.88 was associated with less risk of progression to intubation. Different time points (ranging 2 and 12 hours after HFNO initiation) were used in different studies, with 6 hours point being the most common, showing low sensitivity but acceptable specificity (0.67 and 0.72 respectively).

2. Tissue oxygenation

While oximeters provide data about the peripheral arterial oxygen supply, discrepancies at tissue, cellular and mitochondrial levels do occur. Tissue oxygen tension (tPO_2) refers to the oxygen partial pressure within the interstitial space of a particular tissue reflecting the balance between supply and utilization. Organ specific tools are available including the brain ($PBtO_2$). Intuitively, the management should target perfusion, Hb concentration as well as the respiration. However, in many instances, the first, fastest and easiest response is to increase the fraction of inspired O_2 (FiO_2) and hence pragmatically integrated as a target for any respiratory support.

Monitoring venous oxygen saturation (PVO_2) is another way to assess the adequacy of oxygen supply and extraction. A lower concentration signifies decreased oxygen delivery or higher extraction which can be organ based (e.g., jugular venous oxygen saturation) or systematic (e.g., mixed venous oxygen saturation). Early during shock states, a mixed venous saturation of 70-80% is usually targeted despite downplayed by recent guidelines. Continuous monitoring is possible through fiberoptic catheter that uses reflection spectrophotometry.

3. Capnography

The second function of the respiratory system is to eliminate carbon dioxide (CO_2). This can be measured in the peripheral blood (arterial blood gas) or in the exhaled CO_2 ($PECO_2$) either in intubated or non-intubated patients. Integration into non-invasive devices also does exist.

Expired CO_2 is the endpoint of its production (metabolism), transport (circulation) and elimination (respiration). The arterial partial pressure of CO_2 ($PaCO_2$) in the arterial blood gases (ABG) reflects the relation between CO_2 production and alveolar ventilation. Alveolar ventilation equals minute ventilation (V_{min}) minus the dead space and represents the volume contributing to gas exchange. The dead space is the fraction of the tidal volume (V_T) not participating in the gas exchange whether in the airways (anatomical), alveoli (alveolar) both representing the physiologic dead space in addition to the ventilator circuit (mechanical). The normal anatomic dead space equals approximately 2.2 ml/Kg.

$$\mathbf{PaCO_2 = 0.863 \times [\ V_{CO2} / V_A\ ]}$$

Where V_A is alveolar ventilation, V_{CO2} is CO_2 production, $PaCO_2$ is arterial partial pressure of carbon dioxide

$$\mathbf{V_A = V_{min} \times (1 - V_d/VT)}$$

Where V_{min} is minute ventilation, V_d is the physiologic dead space and VT is the tidal volume

In a resting healthy adult, V_{CO2} is approximately 200 ml/min and V_D/V_t is 0.3, which can be altered in the disease state.

The expired end tidal value (ET_{CO2}) is usually used to monitor the trend of the $PaCO_2$, while the difference between the 2 values can indicate the (physiologic) dead space. This is represented by the Enghoff's Modification of the Bohr Equation

$$\mathbf{Alveolar\ Dead\ space/VT = (PaCO_2 - P_{ETCO2}) / PaCO_2)}$$

Where P_{ETCO2} is the end tidal CO_2, $PaCO_2$ is the arterial partial pressure of CO_2, VT is the tidal volume

The dead space is an independent predictor of mortality in ARDS, and in order to avoid alveolar overdistention became a target for personalized mechanical ventilation. Otherwise, a trace (capnogram) can be displayed which helps to confirm the placement of endotracheal tube (ETT), diagnose bronchospasm, rebreathing and asynchrony, to mention few.

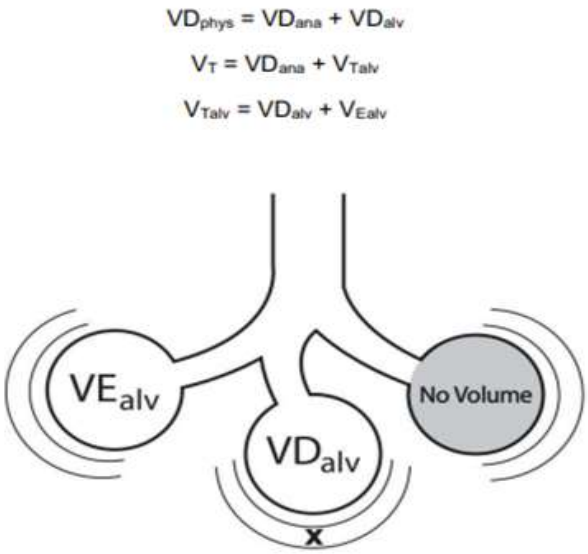


Figure 2: Schematic drawing shows 3 different alveoli with their corresponding capillaries. On the left: well perfused and ventilated alveolus with effective alveolar volume (VE_{alv}), the middle is a ventilated but not perfused alveolus and is considered as alveolar dead space (VD_{alv}), and the right one is an alveolus that is perfused but filled with fluid or collapsed (shunt). From reference 29.

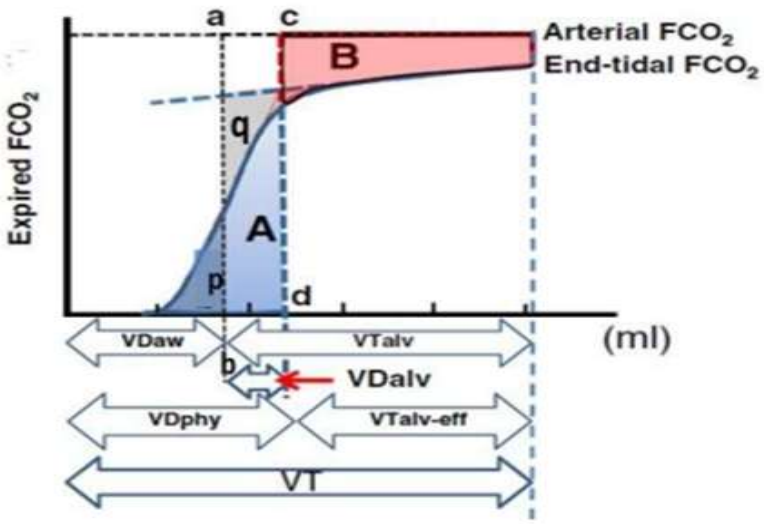


Figure 3: Estimation of dead space and alveolar tidal volume from the volumetric capnometry waveform. The black dashed line a–b defines equal area q and p in phase II. The volume to the left of this line represents the anatomical dead space, while the right of the line is the alveolar tidal volume. The blue dashed line c–d is created so that area A equals area B. The distance from b to d defines alveolar dead space. VDaw: anatomical dead space, VTalv: alveolar tidal volume, VDalv: alveolar dead space, VDphy: physiological dead space, VTalv-eff (VEalv): effective alveolar volume, VT: total tidal volume. Reference: Daoud EG, Franck CL. Alveolar mechanics: A New Concept in Respiratory Monitoring. From reference 29.

Role of Imaging in respiratory monitoring

(Will be covered in detail in separate chapter)

With the exception of Electrical impedance tomography (EIT), imaging lacks the real time continuity of other monitoring devices. Moreover, computed tomography (CT) cannot be applied bedside and needs to carry the risk and workload of transfer. However, CT played a major role to delineate the pathophysiology and phenotypes of ARDS (e.g., baby lung) and still serve as a reference method to validate bedside recruitment tests. Moreover, lung and diaphragmatic ultrasound use is booming as a friendly bedside tool. Respiratory imaging will be revisited in more details in a dedicated chapter of this textbook.

1. Chest X-ray

Chest X-ray (CXR) imaging is a widely used simple diagnostic tool for monitoring lung health and detecting various pulmonary conditions. It provides a two-dimensional image of the chest, allowing visualization of the lungs, heart, mediastinum, airways, blood vessels, and bones. This non-invasive technique is particularly valuable for identifying abnormalities such as pneumonia, lung tumors, tuberculosis, pleural effusion, and chronic obstructive pulmonary disease. While CXR are quick, cost-effective, and involve relatively low radiation exposure, they may not always provide detailed information about subtle or early-stage lung changes. In many instances also, the image quality can be an issue. In such cases, advanced imaging modalities like CT scans may be recommended. Despite its limitations, CXR imaging remains a cornerstone first line tool in lung monitoring, offering critical insights for diagnosis, treatment planning, and follow-up care.

2. Computed tomography (CT)

CT of the chest is a highly advanced imaging modality that provides detailed cross-sectional images of the respiratory system, including the lungs, trachea, bronchi, and pleura. Utilizing X-rays and computer processing, CT chest imaging offers superior spatial resolution and contrast compared to conventional radiography, enabling the detection of subtle abnormalities such as small nodules, early interstitial lung disease, or vascular anomalies (e.g., thromboembolism). High-resolution CT (HRCT) is particularly valuable for evaluating diffuse lung diseases, as it can delineate fine parenchymal structures and patterns of pathology, such as ground-glass opacities, fibrosis, or emphysema. Contrast-enhanced CT is often employed to assess vascular structures, mediastinal masses, or infectious processes, while low-dose CT has become a cornerstone in lung cancer screening for high-risk individuals. The versatility and precision of CT chest imaging make it an indispensable tool in the

diagnosis, staging, and management of a wide range of respiratory conditions, from infections and malignancies to chronic obstructive pulmonary disease and pulmonary embolism. Moreover, the nature and distribution of the structural injury can guide interventions (e.g., proning and recruitment in ARDS, pleural drainage, bronchoscopy in lung collapse, etc.).

3. Magnetic resonance imaging (MRI)

MRI of the respiratory system is a non-invasive imaging technique that utilizes strong magnetic fields and radio waves to generate detailed images of thoracic structures, including the lungs, mediastinum, and chest wall. Unlike CT, MRI does not involve ionizing radiation, making it a safer option for certain patient populations, such as pregnant women or those requiring repeated imaging. MRI excels in soft tissue contrast, allowing for superior visualization of mediastinal and chest wall pathologies, including tumors, vascular anomalies, and inflammatory conditions. Techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) provide functional insights, aiding in the characterization of lesions and assessment of tumor perfusion. However, MRI has limitations in evaluating the lung parenchyma due to low proton density and susceptibility artifacts from air-tissue interfaces, which can reduce image quality. Despite this, advances in ultrashort echo time (UTE) sequences and hyperpolarized gas MRI are expanding its utility in assessing lung structure and function, particularly in diseases like cystic fibrosis or chronic obstructive pulmonary disease (COPD). While not a first-line modality for routine respiratory imaging, MRI plays a complementary role in specific clinical scenarios, offering unique diagnostic information without radiation exposure.

4. Ultrasound

Ultrasound imaging of the respiratory system is a versatile, non-invasive, and radiation-free modality that is particularly useful for evaluating superficial thoracic structures, pleural pathologies, and guiding interventional procedures. The Ultrasound waves (US) become absorbed as they pass through the air; a major barrier for its use. Nevertheless, in lung collapse/consolidation, US becomes an excellent visualizing tool of the de-aerated lungs.

Additionally, US had shown superiority in detecting pleural diseases like pleural effusions, and pneumothorax compared to conventional x-ray imaging. The growing use, skills and availability of US makes it an attractive tool. Serial use can substitute its non-continuity compared to other monitors.

To note that many protocols integrate cardiac and lung ultrasound. Obviously, screening for pulmonary hypertension and right heart strain can guide the respiratory management in many cases (e.g., PEEP setting). Also, the contribution of left heart pathologies in respiratory failure should not be overlooked. Last, heart-lung interaction is a cornerstone in the assessment for fluid responsiveness during shock state commonly associated with acute respiratory failure.

5. Ventilation / Perfusion (V/Q) Scan

V/Q scan is a nuclear medicine imaging technique used to evaluate lung function by assessing airflow (ventilation) and blood flow (perfusion) within the lungs. This test is particularly valuable in diagnosing pulmonary embolism (PE), as it can identify mismatched defects where areas of the lung are ventilated but not perfused, a hallmark of PE. The use of V/Q scans have dropped significantly with the advancement of CT scan technology.

6. Electrical impedance tomography (EIT)

EIT is a non-invasive, radiation-free imaging technique that provides real-time monitoring of lung function by measuring changes in electrical impedance within the thoracic cavity. Different tissues have different electric conductivity and resistance (impedance). Meanwhile, air is a poor conductive. A belt and 16-32 electrodes attached across the 5th-6th intercostal transverse plane measure the surface voltage following the application of an alternating electric current. The captured impedance of a lung slice is subsequently translated into an image with different color scales on a monitor. The display shows a real time image of the lungs but allows also a view of the different zones to detail regional ventilation, collapse and overdistention. EIT has the advantage of being bedside and allowing real time regional imaging offering clinicians valuable guidance.

Advanced monitoring during mechanical ventilation

1. Lung mechanics

Understanding lung physiology and mechanics is fundamental to properly set any respiratory support. The lungs are cyclically exposed to a change in volume. The volume change compared to baseline is called strain. The driving force behind the flow of air form the atmosphere into the lungs (ventilation) is a pressure gradient (driving pressure, ΔP). The lungs behave as an elastic organ which tend to collapse when expanded due to its elastance. Elastance is the change of pressure divided by the change of volume. Compliance (C) is the reciprocal of elastance (E=1/C). The pressure represents lung stress which correlates to the strain, and both are implicated in ventilator induced lung injury (VILI) if certain limits are exceeded

$$\textbf{Stress} = \textbf{K} \times \textbf{Strain}$$

Where K is a constant (specific elastance)

The pressure drop across the respiratory system sums the drop during the air passage in the airways (between the airway opening and the alveoli) and the pressure needed to expand the lungs and the chest wall. An additional minimum pressure is needed to overcome the gas and tissue inertia (temporal acceleration of gas).

$$\Delta P = P_{resistance} + P_{elastance} + P_{inertance}$$

Inertia is usually negligible and omitted for simplicity. ΔP represents the gradient between the pressure at the airway opening (P_{aw}) and any end expiratory pressure within the alveoli (i.e., total PEEP). $P_{resistance}$ can be calculated as the product of the gas flow multiplied by the airway resistance, while the elastance pressure is the product of the volume multiplied by the respiratory system elastance (E_{rs}). All this is represented by the equation of motion:

$$P_{aw} = (R \times F) + (V \times E_{rs}) + PEEP$$

Or

$$P_{aw} = (R \times F) + (V/C_{rs}) + PEEP$$

Where R is resistance, F is flow, E_{rs} is respiratory system elastance, C_{rs} is respiratory system compliance and V is the volume.

The pressure can be generated by the patient's muscular effort, MV or a combination of both. As they are arranged in series, the generated pressures equal their sum. In the spontaneously breathing patient, the muscular contraction generates a negative intrapleural pressure sucking the air from the atmosphere (negative pressure ventilation). In controlled positive pressure ventilation, the ventilator creates a positive pressure at the airway opening (external port of the endotracheal tube) and the gas is pushed to the alveoli. In assisted mechanical ventilation the patient effort adds to the pressure generated by the ventilator.

$$\mathbf{P_{aw} = P_{mus} + P_{vent} = (R \times F) + (V/C_{rs}) + PEEP}$$

Where R is resistance, F is flow, C is respiratory system compliance, and V is volume.

In static conditions of no flow, the contribution of resistance is abolished from the equation (as flow equals zero). This is the reason many indices are measured after applying an inspiratory and expiratory hold (static measurements). When performing an inspiratory hold, the pressure drop from a peak to a plateau pressure ($P_{plateau}$) reflects the $P_{resistance}$. It becomes then possible to calculate the $P_{elastance}$ by subtracting the PEEP from the $P_{plateau}$ (yielding the driving pressure; ΔP). Compliance (static) can then be calculated by dividing VT by ΔP.

$$\mathbf{C_{rs} = VT/\Delta P}$$

ΔP reflects the normalized tidal volume to the respiratory system compliance (C_{rs}); the later in turn correlates with the size of aerated lungs and expectedly associated with ARDS mortality even when delivering V_T or $P_{plateau}$ within the protective range. ΔP is generally recommended to be kept < 15 cmH_2O, and one work showed a 5% increase in mortality with every subsequent increment of 1 cmH_2O.

It was recognized for long time that a high pressure applied to the alveoli can cause injury and air leak (barotrauma), and hence the recommendation to limit $P_{plateau}$. Dreyfus et al subsequently showed that a high P_{aw} is less injurious if achieved by strapping the chest. A significant proportion of P_{aw} in this case was from the external pressure exerted by strapping leading to high pleural pressure (P_{pl}). This led to the better understanding that only the pressure needed to distend the lung tissue (i.e., the transpulmonary pressure (TPP) is responsible for the lung stress and VILI rather than the total pressure applied to the whole respiratory system: lungs and chest wall (i.e., P_{aw}).

$$\mathbf{TPP = P_{alv} - P_{pl}}$$

P_{pl} is dependent on the chest wall elastance (E_{cw}). The total respiratory system elastance sums the lung elastance (E_L) and the chest wall elastance (E_{cw}).

$$\mathbf{E_{rs} = E_L + E_{cw}}$$

TPP cannot be simply estimated from P_{aw} as the lung elastance varies and can range anywhere between 50 to 90% of the total E_{rs}. For example, in ARDS, the pressure needed to oppose the chest wall elastance is in the range of 5–10 cmH_2O but can vary significantly in obese patients or in case of high intra-abdominal pressure. To this end, it is clear that partitioning the distending pressure of the lungs from the chest wall is of major clinical interest. To achieve that, the simplest way is to directly measure the pleural pressure:

$$\mathbf{P_{cw} = P_{pl} - P_{bs}}$$

Where Pcw is the chest wall distending pressure, Ppl is pleural pressure and Pbs is the pressure at the body surface.

While this is not feasible in clinical practice, the pressure in the adjacent esophagus (P_{es}) can be measured by the mean of an esophageal balloon inserted in its lower third (around 35-45 cm from the nostrils) and was widely validated as a surrogate of the P_{pl}. TPP can then be calculated as the difference between the airway pressure and P_{pl} indicating the lung parenchymal stress responsible for lung injury induced either by the ventilator (VILI) or the patient himself (SILI).

$$\mathbf{TPP = P_{alv} - P_{pl}}$$

Or

$$\mathbf{TPP = P_{alv} - P_{es}}$$

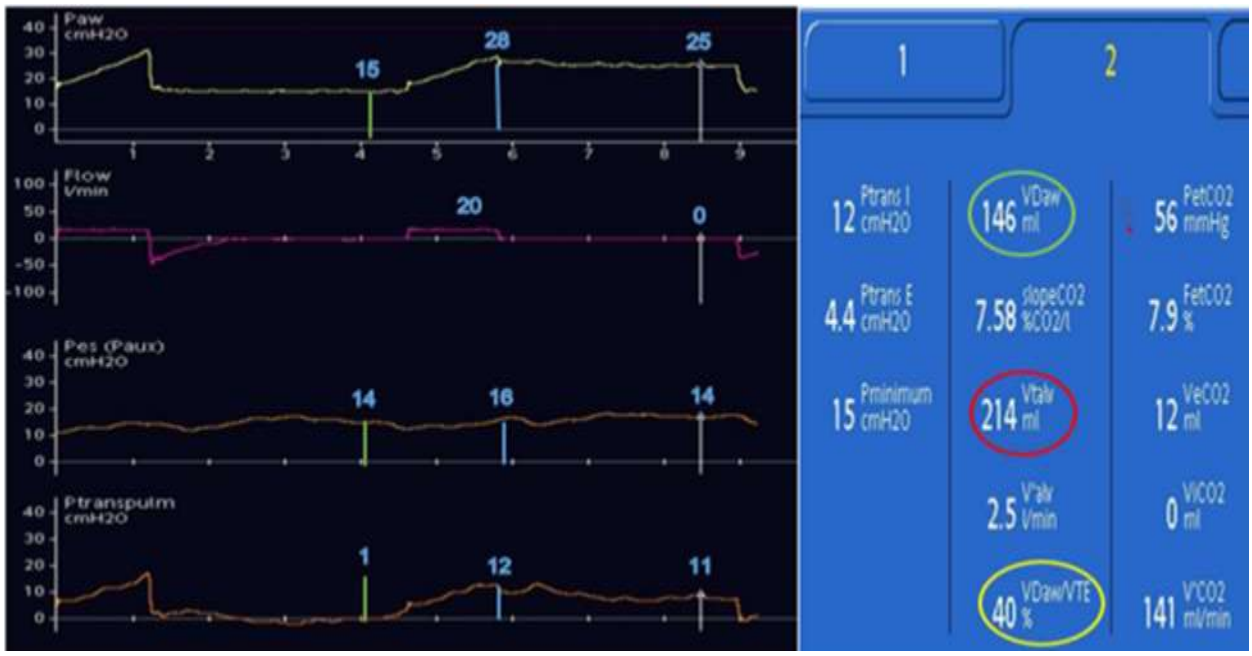


Figure 4: Left graph from a volume-controlled mode: Airway pressure (top in yellow) end expiratory airway pressure 15, peak inspiratory pressure 28, plateau inspiratory pressure 25. Flow (2nd row in pink): continuous flow of 20, end inspiratory and end expiratory flow of zero. Esophageal pressure (3rd 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: VDaw: anatomical dead space, VTalv: alveolar dead space, Dead space/Tidal volume: VDaw/VTE Pressures in cmH_2O, Flow in L/min, Volumes in ml. From reference 58.

2. Esophageal manometry

The principle for Esophageal manometry is described above. Esophageal manometry can serve to:

i. Set the ventilator settings
ii. Monitor the work of breathing (WOB)
iii. Detect patient-ventilator interactions and asynchrony
iv. Research tool to validate less invasive bedside tests

The partition of lung mechanics (pressure and compliance) and measuring TPP are recommended to personalize MV settings and avoid VILI especially in severe ARDS. In such cases, P_{es} is used to personalize P_{aw} and PEEP.

The pleural pressure is not uniform and can vary in the antero-posterior axis, and the directly measured P_{es} was found to correlate more with the pressure in the dependent lung zones. The elastance method to calculate P_{es} can correlate better with the non-dependent areas of the lung.

Inspiratory TPP remains a positive value whether during MV or spontaneous breathing. In the former MV generates a positive P_{aw} while in the later the patient's muscular effort generates a negative P_{pl}. In assisted MV modes, TPP is the sum of both. Vigorous muscular contraction increases the swing the P_{es} (reflecting the muscular pressure P_{mus}) and a value ≥ 15 cmH_2O can be used as a marker of increased work of breathing (WoB) and risks SILI. This can guide the escalation from non-invasive respiratory support including intubation.
The goal during inspiration is to avoid excessive stress (TPP), while during expiration is to avoid atelectasis and atelectotrauma by avoiding negative values.

$$\mathbf{TPP_{end-inspiratory} = P_{plat} - P_{es}}$$

$$\mathbf{TPP_{end-expiratory} = PEEP - P_{es}}$$

(measurements during end-inspiratory and end-expiratory pause respectively)

There is no definite consensus about $TPP_{end\text{-}inspiratory}$, but values ≤ 15-20 cmH_2O can be reasonable. As mentioned above, the difference between the end inspiratory and end expiratory pressure ($P_{plateau}$ - PEEP) is called the driving pressure (ΔP_{rs}) and was correlated with mortality in ARDS. It combines the effect of the tidal volume and compliance/elastance.

$$\mathbf{\Delta P = VT \times E = VT/C_{stat}}$$

Measuring the driving TPP (ΔP_L) can more accurately reflect the tidal lung stress and guide MV. A safe limit in the range 10-12 cmH_2O was suggested by experts but with little consensus.
Unfortunately, and despite its fundamental role, esophageal pressure monitoring is applied in only about 1% of ARDS patients.

3. Ventilator parameters

Modern ventilators may be the most widely used respiratory monitors. In fact, manufacturers compete to offer advanced monitoring options and integrate them into algorithms for ventilator self-actions.

Essentially, the MV operator sets input variables which are translated (through lung mechanics) into output variables (uncontrolled by the operator). Modes are generally divided into volume and pressure modes considered as 2 faces of the same coin, where the relation between the volume and the pressure is governed by lung mechanics (equation of motion).

The displayed data can be set or measured parameters (e.g., RR, VT and pressures) with further calculation of the compliance, resistance and sometimes more advanced parameters (e.g., $P_{0.1}$, leak and intrinsic PEEP). The continuous visual display of the volume, pressure and flow against time as curves (scalars) and against each other: the pressure-volume and flow-pressure loops, are becoming a standard in many ventilators.

The overall aim is to guide the operator to adjust the settings to match the patient's needs, avoiding harm and patient-ventilator asynchrony (PVA). Intelligent closed loop modes are emerging where the ventilators adjust the settings automatically based on the monitored data through pre-programmed algorithms, and the role of clinicians is to set the overall strategy then supervise its application.

Flow curves and loops are particularly useful to detect any mismatch or asynchrony between the patient and ventilator.

4. Alveolar opening and closure pressures

At static states (no flow), the P_{aw} and PEEP reflect the alveolar pressure only if there is a continuity between the proximal airway and the alveoli. In fact, it was shown that around a fifth of ARDS and obese patients exhibit an airway opening pressure (AOP) delineating small airway collapse during expiration. This highlights that collapse can happen not only at the alveolar but also the bronchiolar level leading to a discrepancy between the lungs macro-parameters, as targeted by MV settings, and the micro-environment at the alveolar level. This can lead to misleading measurements even with an expiratory occlusion pressure.

Different alveoli have different opening and closing pressure. The critical closing pressure is the pressure at which alveoli will collapse, while the critical opening pressure (AOP) is the one at which it will (re)open; the last being higher than the former (AOP>closing pressure). In order to avoid atelectotrauma secondary to alveolar cyclic opening and closing, PEEP should be set to keep alveoli open. Ideally, this can be achieved by setting PEEP higher than the closing pressure, despite in clinical practice the AOP is usually the used target, despite some risks of overdistention.

AOP can be detected on the pressure time curves or pressure-volume loops. Using volume mode and slow respiratory rate, the sudden change in the slope of the inspiratory ascending limb (pressure-time curve) signifies the sudden change of compliance from ventilator circuit compliance to the Crs as the alveoli open when reaching the AOP. On a pressure-volume loop, AOP corresponds to the sharp bend of the inspiratory limb (Figure 5). To note, that as recruitment is time as well as pressure dependent, the opening pressure can be better represented by a range of pressure rather than a single value.

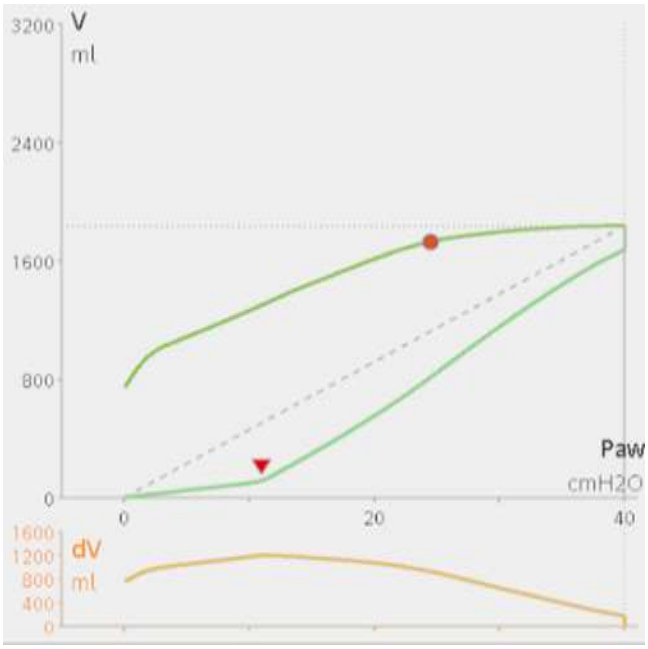


Figure 5: Quasi-static Pressure-Volume curve (top green). Hysteresis volume (bottom yellow). Red arrow points to airway opening pressure, red circle point to point of maximum curvature.

5. Recruitability

'Baby lung' is a term used to describe the lung heterogeneity in ARDS where some pulmonary regions maintain normal inflation while the majority are collapsed. This led to an increased interest in recruiting the collapsed lung units to serve 2 goals:

(1) Improving the gas exchange: more alveoli participating in gas exchange will reduce shunting through the lung, a main mechanism of hypoxemia.

(2) Reducing VILI: When the VT distributes across more units (alveoli), it will produce less strain of each of them. Obviously, keeping more alveoli aerated at the end of expiration means an increase in the end expiratory lung volume (EELV), the denominator of the strain equation (see above).

To achieve that, alveoli need to be opened (inspiratory pressure exceeding the AOP), then prevented from collapsing during expiration (PEEP above the closing pressure). Some alveoli are slower in opening and closing than others (*see time constant*), and as some alveoli are already open and the intervention is applied to the lung as a whole, a recruitment maneuver (RM) can end with either recruitment or overinflation. A third scenario will take place in the consolidated regions (alveoli flooded with exudate or fluid) which will remain closed (resistant to recruitment). If the alveoli then re-close during expiration (PEEP below closing pressure), this will lead to injury by cyclic opening and closing (atelectotrauma).

RM responsiveness is highly variable and difficult to predict by static parameters. One work showed the range of recruitment to be 0 to 40% when increasing the PEEP from 5 to 10 cmH_2O. More importantly, recruitment trials were negative and showed even an increased mortality in compliance based RM combined with high PEEP. Due to those reasons, RM universal application (without pretesting for recruitability) cannot be advised.

CT scan played a major role to describe the 'baby lung' and quantifying the pulmonary tissue and gas volume. The morphologic aeration was then correlated with compliance. While far from being a bedside test (apart from exceptional portable CT scanners), it led to a better understanding of ARDS pathophysiology and offered a tool to validate bedside tests.

6. Recruitment-to-Inflation ratio (R/I ratio)

The concept is to calculate the (de)recruited volume (V_{rec}) during a PEEP reduction (classically from 15 to 5 cmH_2O). By using volume mode with slow respiratory rate (6-8 breaths/min), the VT_e following the PEEP drop will be larger than the previous VT_e as it sums the (de)recruited volume (V_{rec}) (volume lost due additional alveolar collapse if derecruitment happens) plus the reduction in EELV at the lower PEEP (which can be expected by multiplying the $\Delta P \times C_{rs}$ at the low PEEP). V_{rec} can then be calculated as the other variables are known (VT_e, ΔP and C_{rs}) followed by calculating the compliance of the (de)recruited lung (V_{rec}/ΔPEEP drop). R/I ratio is obtained by dividing the (de)recruited lung compliance by the C_{rs} at the lower PEEP. A value > 0.5 was considered a marker of recruitability. While easy to perform bedside, the value can be over or underestimated using different ventilators, and correlate modestly with morphological recruitment on CT scans.

7. Hysteresis and Pressure volume (P/V) curve

Observing the pressure-volume loop, It is easy to notice that the inspiratory and expiratory limbs are not identical (Figure 6). The surface area between the two limbs is called hysteresis demonstrating that the pressure at a given volume is less during expiration than inspiration.

Hysteresis was correlated with compliance (C_{rs}) and the dissipated energy within the lung tissue during respiration. It was postulated the larger the hysteresis the more the lungs' recruitability. This was supported by CT studies showing that hysteresis volume normalized to the maximum volume/pressure of the lung correlates with gas and tissue recruitment. It might be also that this dissipated energy contributes to molecular micro-injury (VILI), a point which needs further investigation.

Some ventilators introduced the P/V method (protective ventilation tool) (Figure 6). coupled by the option to perform a subsequent recruitment maneuver. Using low flow (constant pressure ramp 2-5 cmH_2O/s), the ventilator measures different parameters including the hysteresis volume difference at 20 cmH_2O and the maximum one. The normalized maximal distance (NMD) is the maximum volume difference divided by the maximum volume (V_{max}) reached at maximum pressure (usually 40 cmH_2O). NMD > 41% indicates recruitability and the operator can proceed with RM through a pre-defined algorithm.

To note that both methods (RI and P/V) correlate well and are accepted bedside test for recruitability.

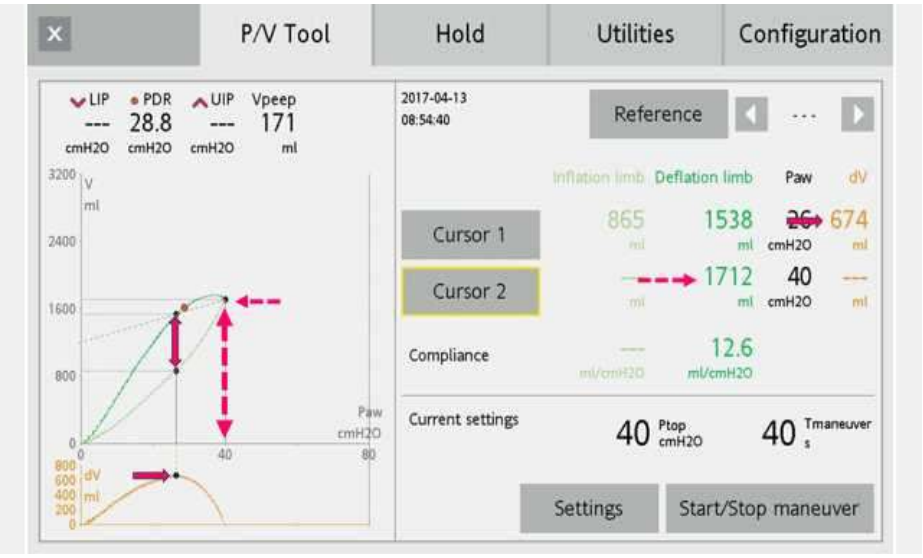


Figure 6: P/V loop showing Normalized Maximum distance and hysteresis. From Hamilton Medical with permission. In this case maximum dV=674 ml, while maximum volume equals 1712 ml. NMD = 674/1712= 39.4%. From reference 80.

8. Positive End Expiratory Pressure (PEEP)

The role of PEEP is to keep the alveoli open during expiration. Applying PEEP can be incremental or decremental (after RM) and needs to be set above the alveolar closing pressure, but the best way to identify the optimum PEEP remains under investigation.

Shortly after the description of ARDS, it was noticed that PEEP was associated with better oxygenation. This was attributed to alveolar recruitment, optimization of gas exchange, reduction in shunt fraction and lung strain (by increasing the end expiratory lung volume (EELV) the denominator of the strain equation = VT/EELV), and the avoidance of tidal atelectotrauma (cyclical opening and closing of the alveoli). On the other hand, PEEP can lead to overdistention, increases the right heart afterload, and pushes the diaphragm down in a less optimum position for contraction. Such factors should be taking into account when setting the PEEP pointing to the complementary role of Critical Care Echocardiography in respiratory monitoring.

Optimum PEEP was a research topic for decades. One recent review identified 22 different investigated methods. The most common are the compliance-based, imaging-based (including EIT, CT and US) and PEEP-FiO_2 tables. Tables are the most simple, categorized mainly into high or low PEEP ones, but lack personalization. Another two common methods are a stepwise increment or decrement to reach the PEEP associated with best compliance or oxygenation (PaO_2 or SpO_2).

In case of bronchospasm and/or short expiratory time, the alveoli do not empty completely leading to the presence of intra-alveolar air (and pressure) at the end of expiration. This is called intrinsic PEEP and is different than the PEEP set by the MV operator. It can be spotted if the expiratory flow does not reach the zero line at the end of expiration (flow-time curve) and can be quantified by performing an expiratory hold. Intrinsic PEEP imposes an additional WOB and can lead to asynchrony by making triggering more difficult (i.e., ineffective efforts). Bronchodilators, selecting the correct size of the endotracheal tune (ETT), and setting the correct expiratory time and inspiratory volume are needed to avoid intrinsic PEEP.

9. Time constant

Time constant (τ) is the product of resistance and compliance. One time constant equals the time needed to inflate or deflate 63% of the total volume. 3τ and 5τ are needed to empty 95% and 99% of the volume and hence can be used to set the expiratory time.

$$\tau = C \times R$$

Where C is compliance (L/cmH_2O) and R is resistance ($cmH_2O/L/s$)

τ is about 0.1 seconds in a normal person. In pathological situations, an increase in compliance or resistance can increase τ. PEEP also was shown to affect the τ. As different alveoli can have different compliance or deflate against different airway resistance, they do have different time constant (i.e., they do not deflate at the same rate; high resistance for example will lead to prolonged time constant and slower filling and deflation).

10. Stress index (SI)

Observing the pressure-time curve during constant flow volume modes in a passive patient (no spontaneous effort) can help to assess lung recruitment or overdistention. An optimum inflation is represented by a linear slope of the inspiratory pressure-time curve. This can be assessed in a qualitative or quantitative way (stress index). An upward concavity is referred to as SI >1 and signifies overdistention. The opposite is a downward concavity (SI <1) indicates tidal recruitment. In such cases, PEEP may need to be adjusted. (Figure 7).

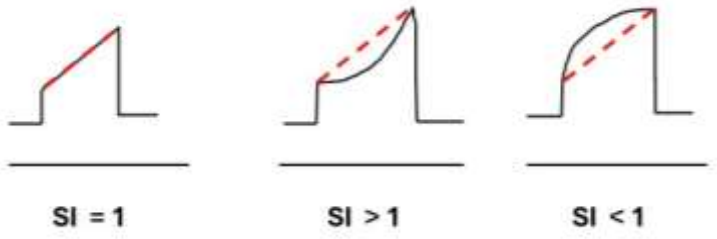


Figure 7: Airway Pressure-Time scalar using the volume controlled mode with constant flow in passive conditions showing different Stress Indexes. The red dashed line represent SI of 1.

11. Mechanical power

VILI involves the contribution of many variables. While the general recommendation is to limit the VT, $P_{plateau}$ and ΔP, a global summative index including all those variables in one equation may be simply more informative. Energy is delivered to the lungs during breathing, but part of it dissipates within the lung tissue (see hysteresis) and is believed to be indulged in the molecular damage of the lung parenchyma.

Experts suggested the mechanical power (MP) as an inclusive physical measure to quantify the driving force for VILI. The equation was founded from the motion equation then multiplied by the RR to describe the energy delivered per minute (j/min). It integrates also the PEEP, but its contribution as

static pressure remains debated. The equation is not simple to calculate but provides a more global picture rather than the single variables. It can be calculated during invasive as well as NIV.
MP validity is based on many studies showing correlation with outcome in different ICU population including non-ARDS. The safe upper limit of MP was suggested to be 12-17 j/min at different time points in different studies. To note that adaptive ventilation modes were shown to be associated with less MP which points to a possible superiority in guarding against VILI. Some ventilators introduced a surrogate or simplified equations to calculate and display MP in volume and pressure modes.

12. Patient-ventilator asynchrony (PVA)

Synchrony between the MV and the patient is essential not only to secure comfort but also for faster weaning and better survival. PVA arises from a mismatch between ventilator assistance and patient's needs either in the form of over or under assistance.
It needs expertise to detect, sometimes only possible with advanced monitoring (e.g., esophageal balloon). It can be simplified by considering the different phases of the respiratory cycle:

Trigger:

- Delayed trigger
- Auto-triggering
- Ineffective effort

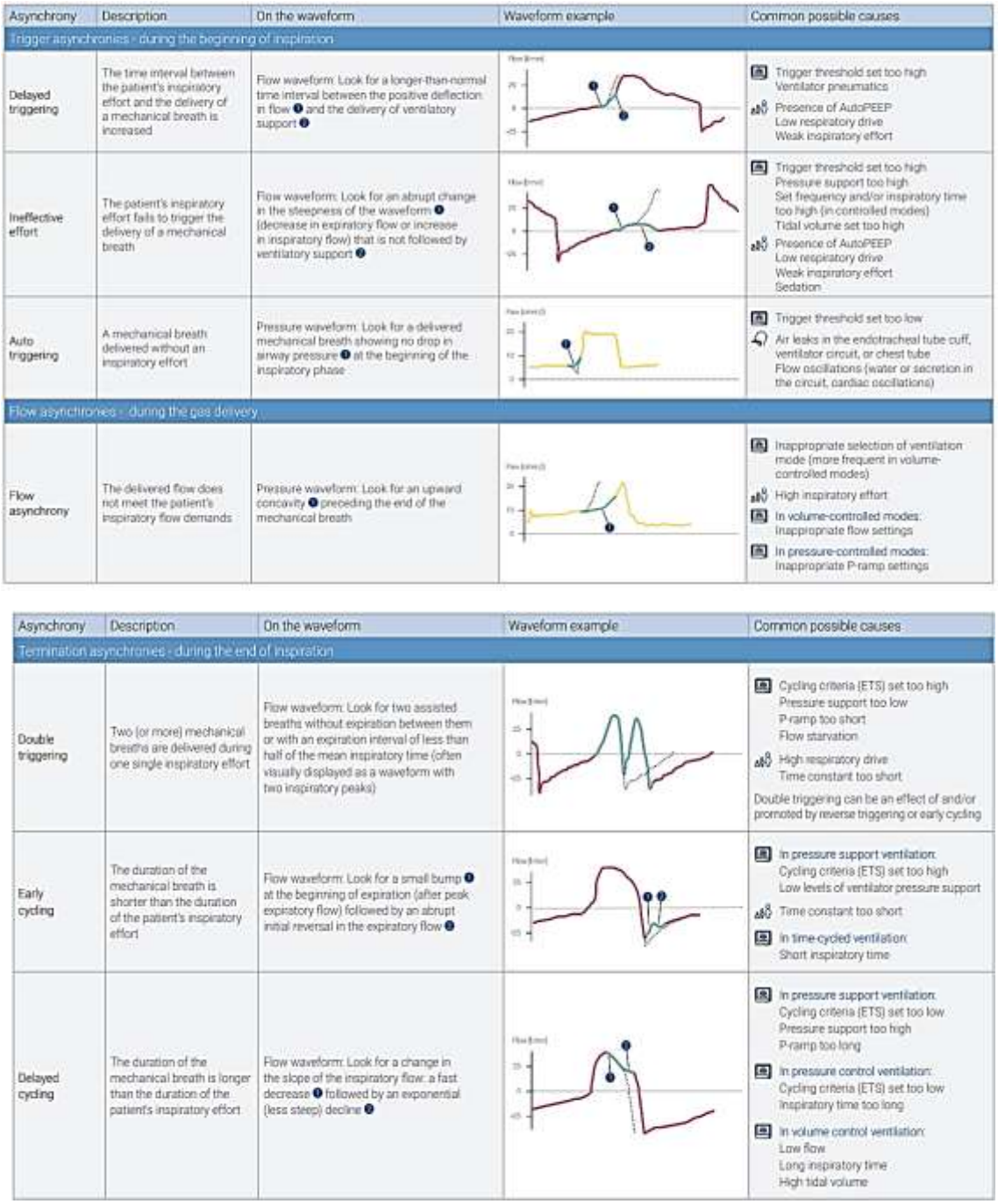
Flow:

- Flow asynchrony (flow starvation)

Cycling (termination of breath):

- Early cycling
- Delayed cycling
- Double triggering
- Reverse triggering

Ineffective effort is the most common followed by double triggering which can be more injurious due to the unintentional increase in VT (breath stacking). Identification is the first step to intervene, mostly by adjusting the ventilator settings. Deeper sedation can be sometimes the last resort but can lead or worsen reverse triggering.



Asynchrony	Description	On the waveform	Waveform example	Common possible causes
Trigger asynchronies - during the beginning of inspiration				
Delayed triggering	The time interval between the patient's inspiratory effort and the delivery of a mechanical breath is increased	Flow waveform: Look for a longer-than-normal time interval between the positive deflection in flow ❶ and the delivery of ventilatory support ❶		Trigger threshold set too high Ventilator pneumatics Presence of AutoPEEP Low respiratory drive Weak inspiratory effort
Ineffective effort	The patient's inspiratory effort fails to trigger the delivery of a mechanical breath	Flow waveform: Look for an abrupt change in the steepness of the waveform ❶ (decrease in expiratory flow or increase in inspiratory flow) that is not followed by ventilatory support ❶		Trigger threshold set too high Pressure support too high Set frequency and/or inspiratory time too high (in controlled modes) Tidal volume set too high Presence of AutoPEEP Low respiratory drive Weak inspiratory effort Sedation
Auto triggering	A mechanical breath delivered without an inspiratory effort	Pressure waveform: Look for a delivered mechanical breath showing no drop in airway pressure ❶ at the beginning of the inspiratory phase		Trigger threshold set too low Air leaks in the endotracheal tube cuff, ventilator circuit, or chest tube Flow oscillations (water or secretion in the circuit, cardiac oscillations)
Flow asynchronies - during the gas delivery				
Flow asynchrony	The delivered flow does not meet the patient's inspiratory flow demands	Pressure waveform: Look for an upward concavity ❶ preceding the end of the mechanical breath		Inappropriate selection of ventilation mode (more frequent in volume-controlled modes) High inspiratory effort In volume-controlled modes: Inappropriate flow settings In pressure-controlled modes: Inappropriate P-ramp settings

Asynchrony	Description	On the waveform	Waveform example	Common possible causes
Termination asynchronies - during the end of inspiration				
Double triggering	Two (or more) mechanical breaths are delivered during one single inspiratory effort	Flow waveform: Look for two assisted breaths without expiration between them or with an expiration interval of less than half of the mean inspiratory time (often visually displayed as a waveform with two inspiratory peaks)		Cycling criteria (ETS) set too high Pressure support too low P-ramp too short Flow starvation High respiratory drive Time constant too short Double triggering can be an effect of and/or promoted by reverse triggering or early cycling
Early cycling	The duration of the mechanical breath is shorter than the duration of the patient's inspiratory effort	Flow waveform: Look for a small bump ❶ at the beginning of expiration (after peak expiratory flow) followed by an abrupt initial reversal in the expiratory flow ❶		In pressure support ventilation: Cycling criteria (ETS) set too high Low levels of ventilator pressure support Time constant too short In time-cycled ventilation: Short inspiratory time
Delayed cycling	The duration of the mechanical breath is longer than the duration of the patient's inspiratory effort	Flow waveform: Look for a change in the slope of the inspiratory flow: a fast decrease ❶ followed by an exponential (less steep) decline ❶		In pressure support ventilation: Cycling criteria (ETS) set too low Pressure support too high P-ramp too long In pressure control ventilation: Cycling criteria (ETS) set too low Inspiratory time too long In volume control ventilation: Low flow Long inspiratory time High tidal volume

Figure 8: Example of ventilator software recognition of dyssynchronies, their recognition, and causes. With permission and credit to Hamilton Medical, Bonaduz, Switzerland. Frome reference 64.

13. Leak

Leak is the difference between the delivered inspired VT (VT_i) and expired VT (VT_e). It is easily measured by the ventilators flow sensors and can happen at the ventilator circuit, endotracheal/tracheostomy tube or at the patient-ventilator interface in NIV. Sometimes, a false leak alarm is due to a dysfunctional sensor.

Leak is mostly inevitable during non-invasive ventilation (NIV) happening around the interface (or from the mouth in case of nasal mask). NIV can compensate for leaks, which is sometimes intentional to help clear CO_2, but a large leak can end with less respiratory support (providing less pressure and VT), patient discomfort and interferes with triggering leading to PVA. This can end by failure of the NIV trial. While NIV has some capacity to compensate for leaks, this differs from device to device. The compensation is better in pressure targeted ventilators but can vary significantly among different devices. Eventually an intervention by the operator is required in the form of adjusting or replacing the masks or modifying the settings.

The endotracheal and tracheostomy tubes have a high-volume low-pressure cuff to guard against air leak and aspiration. During invasive MV, a leak should trigger first an assessment of the correct placement of the endotracheal or tracheostomy tube and the cuff pressure. Cuff pressure should be monitored (target: 20-30 cmH_2O) every 8-12 hours to assure an effective seal but also to avoid pressure damage to the tracheal wall and interfering with its blood flow. New generation of cuff monitors reduce the nursing workload and continuously monitor and adjust the pressure (e.g., Intellicuff, cuff pressure manager). Those monitors can be standalone or integrated into the ventilator itself. A recent meta-analysis showed a benefit in terms of ventilator associated pneumonia (VAP), duration of MV and length of stay in the ICU.

Translaryngeal intubation can lead to laryngeal edema and subsequent failure of extubation in about 3.5% of patients. A cuff leak test is sometimes used to assess the risk of stridor post-extubation by demonstrating either audible leak or observing its volume.

14. Work of breathing

The Work of breathing (WOB) was historically monitored as a sign of respiratory distress and the need to escalate support. WOB correlates with the energy expenditure of the respiratory muscles and is the product of the volume and pressure

$$\mathbf{WOB = \int Pressure \times Volume}$$

Paralleling the equation of motion, it sums 3 components: the work needed to overcome the (1) resistive force, (2) elastic force of the respiratory system and (3) intrinsic PEEP within the alveoli. It ranges between 2.4 to 7.5 J/min or 0.2 to 0.9 J/L . Some recent ventilators display such value based on the pressure time product (PTP) which reflects the pressure generated by the patient's inspiratory

muscles. A mismatch between the respiratory muscle load and capacity will end in respiratory failure unless assistance is applied.

A high central respiratory drive will manifest as an increased WOB. This can reflect the respiratory load (e.g., High CO_2, metabolic reasons) but sometimes it is unrelated (e.g., head injury, pain, anxiety, etc.). This will translate into an increase in the minute volume, through an increase in the muscular effort (and hence V_T) or respiratory rate (RR). When CO_2 rises, an increase in respiratory muscular effort usually precedes an increase in RR. Nevertheless, this depends also on a competent respiratory neuromuscular function as well as the lung mechanics.

While both are signs of respiratory distress, the RR and V_T themselves can furthermore induce/aggravate lung injury whether during MV (VILI) or spontaneous breathing (SILI). Furthermore, vigorous respiratory muscle contractions can precipitate myotrauma and ventilator induced diaphragmatic dysfunction (VIDD), increases the oxygen cost of breathing and consumes a significant part of the cardiac output. Altogether, these risk exhaustion and respiratory arrest. While the threshold to escalate support remains clinically based and difficult to define by simple parameters, undoubtfully a sound monitoring strategy can be of great help.

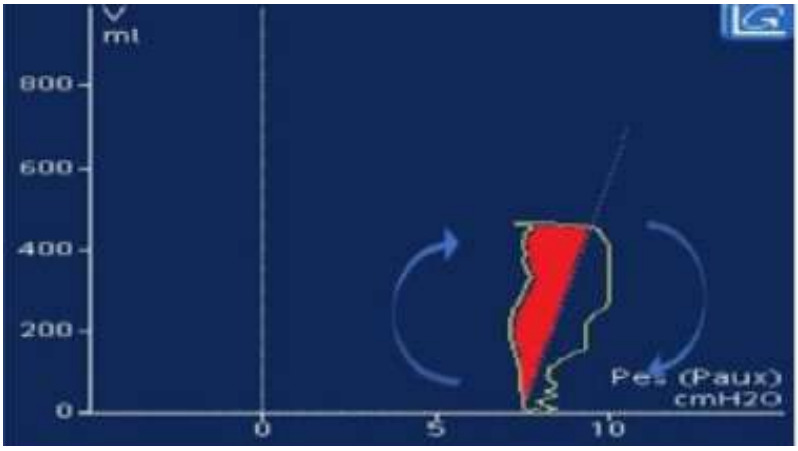


Figure 9: (Pes) in cmH_2O on x-axis versus tidal volume in ml on y-axis. Green dashed line represents the chest wall compliance. Red shaded area is the Campbell diagram representing the inspiratory work of breathing. From reference 85.

15. Pendelluft phenomenon

While ventilators display the V_t they deliver to the lungs, Pendelluft phenomenon refers to the exchange of volume in between the alveoli (movement of air within the lung from alveoli to alveoli without a change in VT). It usually happens in injured lungs during spontaneous effort from non-dependent to dependent areas. The reason is the non-uniform transmission of the diaphragmatic contraction (differential P_{pl}) during spontaneous efforts. It follows that some alveoli will be subject to more strain, even with a VT within the target range. This highlights the value of regional monitoring of ventilation (see EIT in respiratory imaging).

16. Neuromuscular function

A competent neuromuscular function is pivotal to counterbalance the respiratory load. It needs to be monitored probably from the start till the cure of ARF; nevertheless, 2 occasions are of greatest interest: (1) in the deteriorating patient leading to respiratory failure, and (2) when worsening or de novo muscle weakness risks weaning failure from MV. In the former, emergency situations herald effective monitoring during patients' distress and usually out of ICU. Following the institution of mechanical ventilation, diaphragmatic injury can happen after a few days of controlled ventilation which is associated with prolonged weaning and worse outcome.

Monitoring during weaning was much more investigated. The shift from controlled mode (total work done by the ventilator) to an assisted mode (e.g., pressure support ventilation, PSV) means the patient starts to share the load with the ventilator, which requires close observation. Both under and over assistance are associated with harm, and VILI/SILI are still possible as lungs usually did not heal completely. A mismatch between the patient and ventilator duration of insufflation can lead to double triggering or early cycling (PVA). So, the challenge here is to set the appropriate amount and duration of support, impossible without real time information about the respiratory drive, lung mechanics and most importantly the neuromuscular function.

A. Airway Occlusion Pressure at 100 msec ($P_{0.1}$)

$P_{0.1}$ refers to the P_{aw} at 100 msec after the start of inspiration while the respiratory circuit is occluded (Figure 9). The perception of any respiratory load is absent at that time point. As the airway is occluded, both the flow and volume equal zero, excluding any contribution of lung mechanics (i.e., resistance and elastance omitted). Its better correlation with the end tidal CO_2 rather than the minute ventilation supports its correlation to the respiratory drive. $P_{0.1}$ remains preserved even in muscle weakness if the patient can trigger. Last, while intrinsic PEEP can

theoretically cause a delay in triggering, $P_{0.1}$ was validated in case of hyperinflation with good accuracy.

Most ventilators provide $P_{0.1}$ monitoring ideally through end-expiratory occlusion despite its site (airway vs ventilatory circuit) and duration can differ affecting its value. Classically, it is performed as an intermittent manoeuvre and it is recommended to average 3-5 values. Some ventilators provide continuous breath per breath monitoring which permits the observation of the trend over time and with different levels of support. In these cases, occlusion is not possible with every breath and the value is extrapolated from the pressure curve. This risks inaccuracy (usually underestimation) and the operators should be mindful of the different methodologies between devices and their effect on the reference range.

$P_{0.1}$ ranges 0.5-1.5 cmH2O in healthy people, while values >3.5 cmH2O was generally used to indicate increased drive during MV. It is of particular value during the sedation weaning and transition from controlled to assisted ventilation. A high $P_{0.1}$ was shown to be associated with weaning failure, and in hyperinflated lungs, it can guide PEEP titration (drop in $P_{0.1}$ indicates less intrinsic PEEP). $P_{0.1}$ can help to differentiate double triggering (high value) from reverse triggering (low value).

B. Electrical activity of the diaphragm (EAdi)

Monitoring the electrical activity of the respiratory neuromuscular function (electromyography) can be achieved via electrodes placed on the skin (surface electromyography, sEMG) or mounted on a nasogastric tube. While sEMG carries the additional benefit of monitoring the extra-diaphragmatic respiratory muscles, being non-invasive, but its application is technically challenging and needs high level of expertise limiting its use currently to research.

The diaphragm contributes 75-90% of the respiratory work. The electrical activity of the diaphragm (EAdi) is the sum of the diaphragmatic muscle fibers action potentials. The captured amplitude represents the diaphragmatic neural excitation (phrenic nerve activity) partially reflecting the central drive and its translation into a contraction magnitude per breath. The normal value in healthy people at rest is approximately 10 μV.

The commercially available Neurally Adjusted Ventilatory Assist (NAVA) uses EAdi for better synchronization of the mechanical breath with the patient’s neural inspiration and expiration.

EAdi is readily displayed on the ventilator screen and the operator sets a gain constant called the NAVA level which the ventilator translates into P_{aw}.

P_{aw} (cmH_2O) = EAdi (µV). NAVA level (cmH_2O/µV)

Monitoring EAdi provides useful information to the clinician during weaning from MV, as it was shown that an early increase in its value was associated with weaning failure. The pressure generated by the respiratory muscles, usually measured by esophageal balloons, showed close correlation with EAdi in the single patient.

The relation between the electric activity and the generated pressure and volume can provide even more insight. Neuromechanical efficiency (NME) offers an estimation of the inspiratory effort and is calculated as delta P_{aw} divided by EAdi during an end-expiratory occlusion. Last, the ability to transform the electric activity into tidal volume is called Neuro-ventilatory efficiency index (NVE).

NVE (ml/µV) = VT/EAdi

EAdi/NAVA use can be affected by neurological injury of either the central respiratory centers or phrenic nerves. It measures only the diaphragmatic function, and liable to technical pitfalls including catheter positioning and signal interference (e.g., cardiac oscillations). It can be used during invasive or non-invasive ventilation and can help to synchronize the triggering and cycling of the breath.

C. Trans-diaphragmatic pressure (Pdi)

Measuring the diaphragmatic force is another way to assess the diaphragmatic function. As Pressure equals force divided by the surface area, the pressure difference across the diaphragm is a valid measurement.

Transdiaphragmatic pressure (Pdi) is the difference between the pleural pressure and abdominal pressure

$$\mathbf{Pdi = Ppl - Pab}$$

An esophageal balloon with supplementary gastric balloon can measure th surrogate values of the P_{es} and gastric pressure (P_{ga}):

$$\mathbf{Pdi = P_{es} - P_{ga}}$$

Despite Pdi remains a reference tool, its use is largely confined to research. It can be affected by the abdominal muscle contraction and lung volume (the change of the position and curvature of the diaphragm affect its length and hence its force).

D. Respiratory muscle pressure (P_{mus})

Assessing the pressure generated by the respiratory muscles is the cornerstone to assess neuromuscular function. P_{aw} is readily shown on the ventilator screen but does not reflect P_{mus}. In fact, many derived measurements can be used bedside.

P_{mus} is the reference for muscular assessment and can be computed from the motion equation if other variables are known (see above). This requires esophageal pressure monitoring to calculate the chest wall elastance (E_{cw}) by dividing the ΔP_{es} by the VT ($E_{cw} = \Delta P_{es}/VT$). When the airway is occluded at the end of inspiration, the muscles become relaxed and their pressure is transmitted to the inner structures, increasing P_{pl}, P_{alv} and P_{ao}. Then the P_{mus} can be calculated.

$$\mathbf{P_{mus} = V_t \times E_{cw} - \Delta P_{es}}$$

Such airway occlusion at the end of inspiration is also the basis to calculate the pressure muscle index (PMI) (see below). P_{mus} normally ranges between 3-15 cm H_2O.

E. Pressure Muscle Index (PMI):

During PSV, the patient's muscles are generating a negative pressure usually measured by esophageal manometry. End-inspiratory hold was classically used to abolish the effect of flow and resistive pressure (statis vs dynamic mechanics). However, it was shown that performing an end-inspiratory hold during PSV leading to muscle relaxation can reveal the pressure exerted by the muscles. To be valid, the maneuver needs to create a new constant plateau (flat plateau> 2 sec) with no visible inspiratory or expiratory effort. PMI can be measured as the difference between the end-inspiratory plateau and the sum of PS and PEEP. (Figure 10).

$$\mathbf{PMI = P_{end\text{-}insp\ plateau} - (PS+PEEP)}$$

Studies showed good correlation with P_{mus}, PTP, and other esophageal pressure-derived effort variables. The normal value ranges 0-2 cmH_2O, while a value > 6 cmH_2O denotes under-assistance and < 2 cmH_2O means over-assistance.

F. Maximum Inspiratory Pressure (MIP) and Maximum Expiratory Pressure (MEP)

MIP (PImax) and MEP (PEmax) are the peak pressures reached during maximum inspiration and expiration respectively. They need patient cooperation for valid testing and are recommended by respiratory societies as a global marker of muscular strength.
MIP indicates inspiratory muscle strength. In ventilated patients, end expiratory occlusion is used to measure the generated inspiratory pressure and hence the name: Occlusion pressure (P_{occ}) (see below).

MEP also indicates muscle strength but it is particularly important to assess coughing and secretion clearance, a fundamental prerequisite for successful extubation especially in patients with muscle weakness. The classical MEP (cooperative sitting patient with a nose clip) is not possible in the ventilated ICU patient. Instead, it was suggested to measure the pressure and flow during induced cough (Cough peak flow (CPF)). CPF value depends on both the inspiratory and expiratory muscle function, lung and airway mechanics, age and the glottic closure (impossible in intubated patients). This is usually tested after a successful spontaneous breathing trial (SBT) in non-sedated patients when the best flow velocity can be recorded by the ventilator (or by an external device). A value >60 L/min at the ETT level was suggested to predict successful extubation. It can also be used before decannulation of tracheostomies.

G. Occlusion Pressure (P_{occ})

In the ICU, many ventilators offer the option to perform the maximum inspiratory pressure (MIP) in intubated patients, but it requires cooperation and repeated measurements. It is another occlusion pressure (like $P_{0.1}$) requiring end-expiratory hold. While $P_{0.1}$ captures the pressure earlier at 0.1 sec, P_{occ} will represent the delta change in pressure between end expiration (PEEP) and the negative peak (trough) during occlusion. (Figure 10)

$$\mathbf{P_{occ} = P_{trough} - PEEP}$$

Technical differences between manufacturers do exist which includes the duration of the occlusion and the starting volume (residual volume vs functional residual capacity). The normal range is considered between -3 and -15 cmH_2O. A high value suggest weakness is less likely, while a low value can be biased by technical factors or poor effort.

It represents the muscular effort and total stress of the lungs but the main interest in P_{occ} may stem from the validated calculation of P_{mus} from its value:

$$\mathbf{P_{mus} = K.\ P_{occ} = -3/4.P_{occ}}$$

K is a constant which was shown to be equal to – ¾

Furthermore, knowing P_{mus} means that the dynamic TPP can be calculated:

$$\mathbf{TPP_{(dyn)} = (P_{peak} - PEEP) - (2/3\ P_{occ})}$$

Online calculator can be found at: https://societymechanicalventilation.org/calculators/

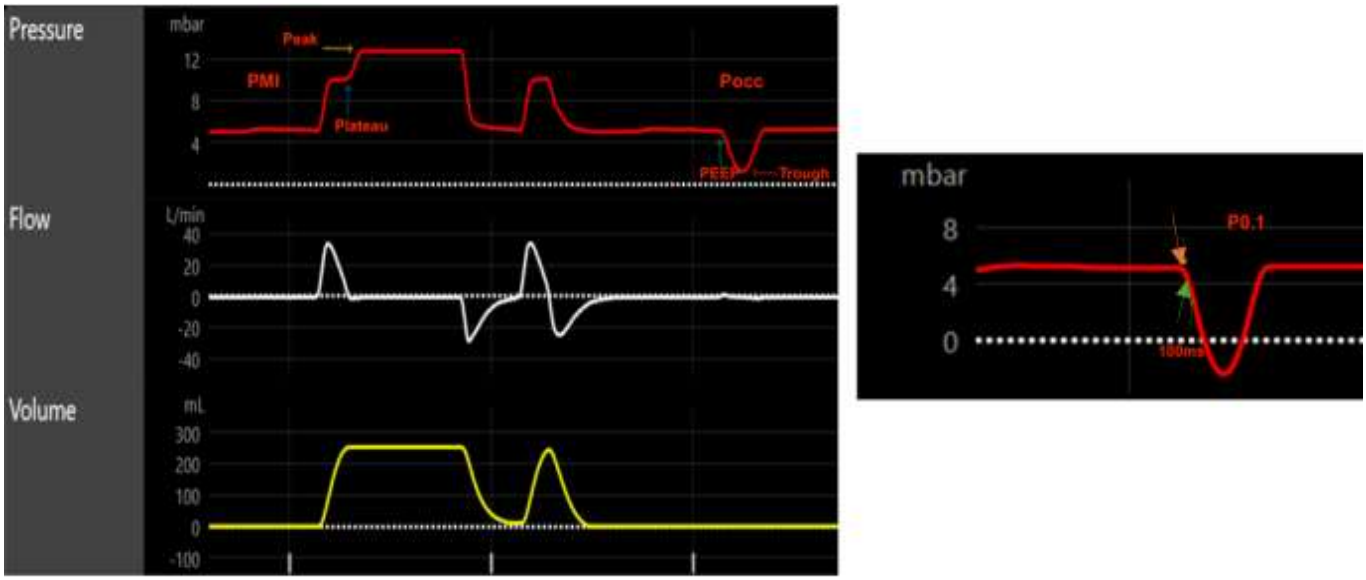


Figure10: Ventilator interface showing inspiratory effort. Key features are labelled for measurement of PMI (during inspiratory hold), P_{occ} and $P_{0.1}$ (measuring during expiratory hold). Arrows denote the beginning and end of the maneuver.

Conclusion

A personalized approach of respiratory support is not possible without a multifaceted monitoring strategy. Different tools can be used concomitantly or subsequently in different phases of the disease, particularly in the most complex cases, namely (but not exclusively) ARDS.

The generated data should be interpreted not only correctly but also in a timely manner. To this end, a deep understanding of the respiratory physiology, underlying pathology, monitoring principles and the limits of a growing number of tools is becoming a challenging mission for clinicians. The inclination to use machine learning and artificial intelligence for automatic closed loop adjustment is promising but will not replace human supervision at least in the near future.

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