



Monitoring the Patient During Assisted Ventilation

6

Alice Grassi, Irene Telias, and Giacomo Bellani

During Assisted Mechanical Ventilation, the work of breathing is shared between the patient's muscles and the ventilator. The steady advancement in technology over the last decades led to the development of several modes of Assisted Ventilation (see Chap. 5), primarily oriented towards improving the patient–ventilator interaction. Assisted ventilation may be applied at different stages of the disease: still in the acute phase, as a transition from controlled ventilation, later on in the weaning phase or chronically.

Allowing a patient to breath spontaneously, while invasively ventilated, has some obvious physiological advantages and it is a step towards re-establishing a completely normal respiratory physiology, when all the work of breathing is supported by the patient's respiratory muscles. Assisted ventilation, as compared to fully controlled ventilation, is associated with decreased sedation requirement (clearly avoiding muscle paralysis) [1], preserved diaphragmatic trophism and prevention of

A. Grassi

Department of Anesthesiology and Pain Medicine, University of Toronto,
Toronto, ON, Canada

I. Telias

Interdepartmental Division of Critical Care Medicine, University of Toronto,
Toronto, ON, Canada

Division of Respiriology, Department of Medicine, University Health Network and Sinai
Health System, Toronto, ON, Canada

Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St.
Michael's Hospital, Toronto, ON, Canada

G. Bellani (✉)

School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy

Department of Emergency and Intensive Care, ASST Monza, San Gerardo Hospital,
Monza, Italy

e-mail: giacomo.bellani1@unimib.it

dysfunction [2, 3]. On the other side, assisted ventilation, not differently from controlled ventilation, can expose the lung parenchyma to excessive stress and strain, leading to lung injury, but with some peculiar mechanisms, which led to the concept of “Patient Self-Inflicted Lung Injury” [4]. The deleterious effects of vigorous inspiratory efforts on lung parenchyma can be summarized as follows [5]:

1. Delivery of high tidal volumes, not completely under control of the clinician,
2. Local overdistension in the diaphragmatic regions due to pendelluft phenomenon,
3. Increase of transmural vascular pressure with increased risk of pulmonary edema,
4. Asynchronies, especially breath stacking causing overdistension.

Outside the lung, preliminary evidences are showing that diaphragm injury can occur not only due to inactivity but also to over activity and/or eccentric contraction (myotrauma) [3].

Finally, the changes in intrathoracic pressures due to mechanical insufflation associated to inspiratory efforts can lead, on one hand to improved preload, but, at the same time increased ventricular afterload, with a balance between favorable and adverse hemodynamic effects [6].

Assisted ventilation is very delicate, especially in patients with compromised lungs and it is hence clear how monitoring all the components involved is crucial to take advantage of the benefits while avoiding the risks.

6.1 Inspiratory Effort

Monitoring the inspiratory effort generated by the patient during assisted ventilation serves multiple purposes. First, it can give an indication of adequacy of the level of respiratory support and of sedation. Second, the change in respiratory effort during a trial of weaning from the ventilator may help in predicting the failure or success of such a trial [7]. Third, an insufficient or excessive level of inspiratory effort is related to diaphragm atrophy or dysfunction [3]. Fourth, in conditions of hemodynamic compromise, the effort done by the inspiratory muscles can be a significant source of oxygen consumption and therefore should be reduced by means of sedation and/or paralysis [8, 9]. Finally, it allows the calculation of the total pressure applied to the respiratory system, as described more in detail in the following.

6.1.1 Esophageal Pressure Derived Measurements

The measurement of the total work of breathing (WOB) requires an esophageal pressure (Pes) catheter. While the mechanical WOB is formally calculated as the area enclosed in a pressure–volume loop of the respiratory cycle (Campbell diagram, Fig. 6.1a), this does not account for the isometric contraction of the respiratory muscles and the duration of the effort. This limitation is overcome by the

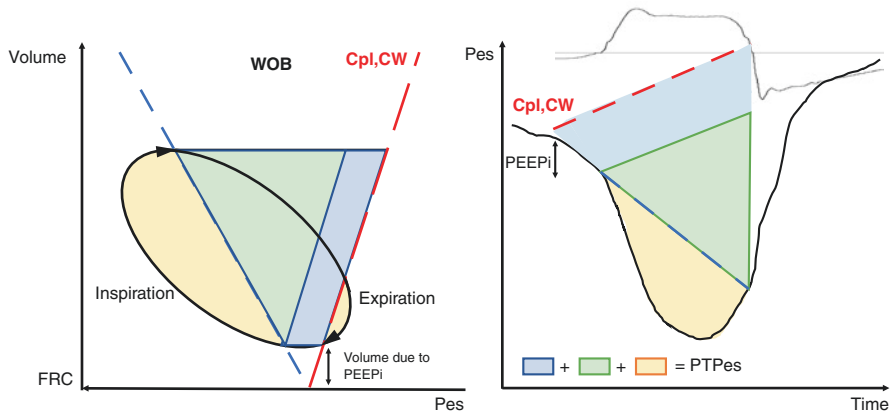


Fig. 6.1 The left panel shows the Campbell diagram of esophageal pressure plotted with lung volume. The intrinsic PEEP (PEEPi) is the pressure generated without generating any inspiratory volume. The work of breathing (WOB) is the integral of Muscle Pressure (Pmus). The red dashed line represents the passive recoil of the chest wall. The WOB has three components: resistive (yellow area during the inspiration phase), elastic (green area), and related to PEEPi (blue area). The small yellow area in the expiration phase represents the active expiratory WOB. The right panel shows the Pressure Time Product (PTP), which is the area under Pmus over the inspiratory time. As the WOB, the PTPes has three different components: resistive (yellow), elastic (green), and due to PEEPi (blue). The PTP is calculated in the inspiratory phase, i.e. between the two points with zero flow. Flow tracing is shown above Pes

esophageal Pressure Time Product (PTPes), which is the integral of the muscular pressure (Pmus) over time (Fig. 6.1b), which correlates well with the energy spent by the inspiratory muscles. Pmus is measured as the difference between the static recoil pressure of the chest wall and the total Pes. Normal values are between 50 and 150 $\text{cmH}_2\text{O}\cdot\text{s}/\text{min}$ [10].

Despite being less accurate and more simplistic than WOB or PTPes, estimating the inspiratory effort by Pes swing (maximum inspiratory deflection of Pes starting from end expiration) is more feasible at the bedside. Targeting a normal value of maximal inspiratory Pmus of 5 to 10 cmH_2O (which, with normally low chest wall elastance, corresponds to a Pes swing of 3 to 8 cmH_2O) seems reasonable to avoid excessive lung stress and diaphragm atrophy [11]. A recent study aimed at finding predictors of non-invasive ventilation success or failure, showed that intubation was avoided in those patients in whom the application of non-invasive ventilation led to a significant reduction of Pes swing towards more “physiological” values [12].

6.1.2 Tidal Volume and Respiratory Rate

Respiratory rate and tidal volume are poor estimates of effort in ventilated patients. They are influenced by respiratory mechanics and respiratory muscle weakness. Also, resting respiratory rate in critically ill subjects is high, does not follow

respiratory drive within a wide range (PaCO_2 from 23 to 45 mmHg) [13], and is independently modified by other factors [14, 15].

Nonetheless, a respiratory rate lower than 17 during pressure support can diagnose low drive and effort [16]. Increase in tidal volume without changing support reflects higher effort. However, a decrease in effort is not followed by a decrease in tidal volume below a certain threshold during pressure support. The Rapid Shallow Breathing Index (RSBI) combines these variables describing patient's breathing pattern. It was developed [17] for early prediction of weaning failure during a spontaneous breathing trial on T-piece (value >105 breaths/min/L) and suggestive of a fatiguing breathing pattern [18].

6.1.3 p0.1

The p0.1 is the drop in pressure generated by the patient in the first 100 ms of an inspiratory effort, during a short airway occlusion. It is an estimate of the patient's central respiratory drive, because there is no reaction to the mechanical load at the very beginning of an expiratory hold. Moreover, it is independent from airway resistances, because it is measured with zero air flow. Given the inter-breath variability of p0.1, an average of 3–4 measurements should be taken for a correct representation of respiratory drive. P0.1 in healthy subjects is between 0.5 and 1.5 cmH_2O [19]. One of the advantages of p0.1 is that it is easily measured by most of the available ICU ventilators either on a breath-to-breath basis (possibly underestimating the real value with large inspiratory efforts) or with a brief expiratory hold. A recent study [20] validated the p0.1 as measured by the commercial ventilators and confirmed its role as a measure of the patient's respiratory drive and work of breathing. Particularly, a threshold of 1 cmH_2O is used to determine a low inspiratory effort ($\text{PTP}/\text{min} < 50 \text{ cmH}_2\text{O}^*\text{s}/\text{min}$), while a value of p0.1 higher than 3.5 to 4 cmH_2O corresponds to a high inspiratory effort ($\text{PTP}/\text{min} > 200$ to $300 \text{ cmH}_2\text{O}^*\text{s}/\text{min}$). Despite no value of high or low p0.1 was clearly correlated to weaning failure, these thresholds can be used in clinical practice to follow the responses in patients' efforts to change in respiratory support [20].

6.1.4 Occlusion Pressure

Another indication about the inspiratory effort can be obtained from the inspiratory depression of the airway pressure trace during a longer (as compared to p0.1) expiratory hold (ΔPocc), as shown in Fig. 6.2a. From ΔPocc , an accurate prediction of Pmus is possible through a simple calculation ($\text{Predicted Pmus} = -3/4 * \Delta\text{Pocc}$). When performing this simple maneuver at the bedside, an average of three values should be calculated. The target of predicted Pmus for a safe ventilation is the same as for Pmus , 5–10 cmH_2O [21].

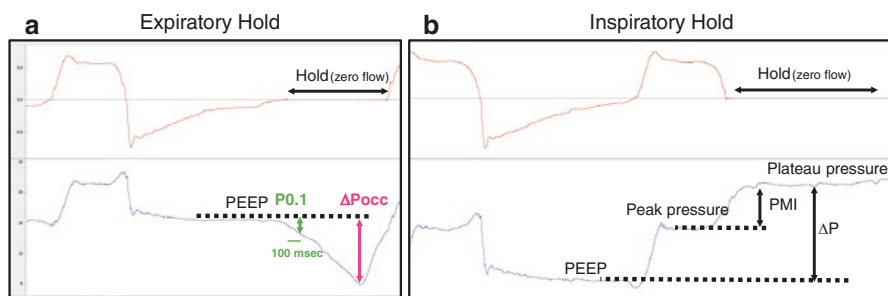


Fig. 6.2 Panel **a** shows an expiratory hold during pressure support ventilation. The expiratory occlusion pressure (ΔP_{occ}) in pink is the difference between PEEP and the nadir of airway pressure during the hold. The airway occlusion pressure (P0.1) in green is the drop in airway pressure during the first 100 ms of the occlusion. Panel **b** shows an inspiratory hold during Pressure Support Ventilation. The airway pressure during the plateau is flat, the airflow is zero and therefore the plateau is readable. The measurement derived from an inspiratory hold are: Plateau Pressure, Pressure Muscle Index (PMI=Plateau minus Peak pressure), Driving Pressure (ΔP)

6.1.5 Pressure Muscle Index

Inspiratory effort can also be estimated through an inspiratory hold with a technique described in the 1990s [22, 23]. If, during the hold, the patient's respiratory muscles relax, the pressure that they were generating at end inspiration will be "released" inside the airways and, in a condition of zero flow, will appear as an additional pressure on the airway pressure tracing, in the form of a plateau pressure (Fig. 6.2b), which, as better outlined below, is required to be flat, in order to be "readable." The difference between the plateau and the peak pressure, the so-called Pressure Muscle Index (PMI), was shown to tightly correlate with the muscular pressure at end inspiration as measured by a Pes catheter [23].

6.1.6 Diaphragm Electrical Activity

The electrical activity of the crural diaphragm (Edi) can be monitored with a feeding tube arranged with eight electrodes on its distal end: while mainly devised to provide Neurally Adjusted Ventilatory Assist (Chap. 7), this is also a valuable monitoring tool. As compared to monitoring the flow and pressure tracings on the ventilator, the electrical activation of the diaphragm is obviously closer in time to the output of the respiratory centers, being a measure of respiratory drive [24]. Edi was shown to tightly correlate with transdiaphragmatic pressure and to change proportionally with the level of respiratory assist [25]. Edi can be used to evaluate "graphically" the patient presence of asynchronies [26], intrinsic PEEP [27], reverse trigger [28] as also shown in Chap. 37. Moreover, it has been suggested that the ratio between the drop in airway pressure and Edi during one expiratory occlusion (sometimes named Neuro-Muscular Efficiency) allows to translate the Edi value into Pmus during regular tidal ventilation [29], as depicted in Fig. 6.3.

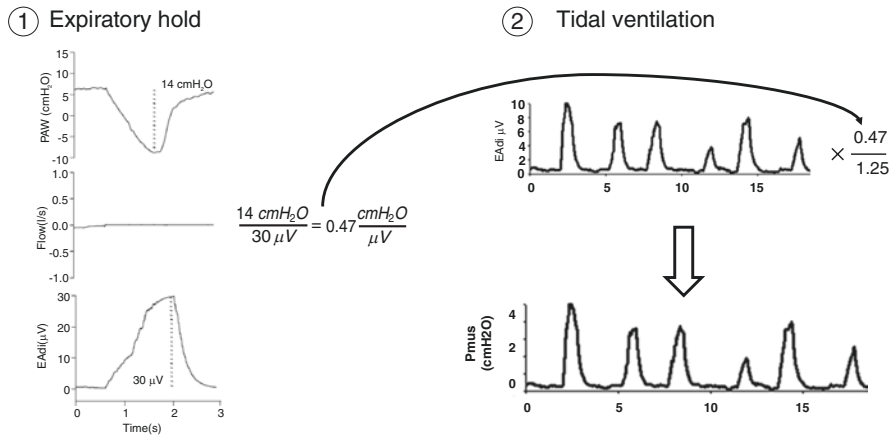


Fig. 6.3 Technique to obtain muscle pressure (Pmus) from Electrical Activity of the diaphragm (Eadi). At first (Panel 1) during an expiratory hold, compute the ratio between the pressure of the inspiratory effort and the Eadi amplitude corresponding to the swing. This ratio (named Neuromuscular Coupling or Pressure/Eadi Index, PEI) has dimensions of $\text{cmH}_2\text{O}/\mu\text{V}$ and is supposed to indicate the amount of pressure (in cmH_2O) that the respiratory muscles of the patients are generating for each microvolt of electrical activity. This ratio (divided by 1.25 to account for the more favorable contraction of the diaphragm during isometric contraction) is then used (Panel B) as a conversion factor, in the subsequent breaths to convert Eadi in Pmus

6.2 Total Pressure Distending the Respiratory System

During assisted ventilation, both the positive pressure imposed by the ventilator (set by the clinician) and the negative pressure generated by the patient's muscles contribute to overcome the resistive and elastic pressures of the respiratory system, leading to increase in lung volume. Hence considering only the pressures displayed on the ventilator screen (peak pressure and PEEP) does not provide a truthful representation.

The patient inspiratory effort determines the amount of negative pleural pressure generated in every breath, which “pulls” the alveoli from outside. A direct measurement of this pressure is provided by a Pes catheter, surrogating pleural pressure. Transpulmonary pressure (P_L) is the difference between Paw and Pes and it estimates the stress applied on the alveoli at any given moment. An experimental study [30] clearly showed that strong inspiratory efforts worsen lung injury despite limiting the positive pressure imposed by the mechanical ventilator to lower than 30 cmH_2O , demonstrating that a component of the pressure equation is hidden to the clinician only monitoring the instantaneous Paw shown by the ventilator.

Many factors though should be taken into consideration when using P_L as a measure for lung stress.

Dynamic P_L is the maximum P_L during an inspiratory effort. This value also includes the pressure generated to overcome the airflow resistance. While on one

hand the resistive component is not dissipated across the alveolar wall, it may lead to absolute negative value alveolar pressure, possibly injurious. Moreover, P_L is normally calculated under static conditions during controlled ventilation and this should be taken into account when comparing assisted versus controlled ventilation [31]. Finally, P_L is a global measurement and does not reflect regional differences in lung properties, which might lead to regional heterogeneity, as outlined below.

Safe limits for P_L during spontaneous breathing are not fully established yet, but a ΔP_L of 15 cmH₂O has been suggested as threshold not to be exceeded for a safer Assisted ventilation [11].

While the Pes catheter is the most direct way of estimating P_L , it must be recognized that its use in clinical practice is not widespread.

Alternative methods of estimating the total pressure distending the respiratory system have been developed, by means of the mechanical ventilator tracings.

The inspiratory hold described above, and shown in Fig. 6.2b as a means of measuring PMI reveals a plateau pressure which can be higher than the airway peak pressure, since it includes both the pressure generated by the ventilator plus the muscular pressure released by the inspiratory muscles [32–34]. This Plateau pressure has exactly the same meaning as when measured during controlled ventilation, allowing to compute static Driving Pressure (Plateau Pressure-PEEP). Intuitively, performing an inspiratory hold during Assisted ventilation is more complex and uncertain than in passive conditions, because the patient's muscles are active and the plateau would not be reliable in the absence of relaxation. Approximately 20% of patients will have unreadable traces during Assisted ventilation, especially the ones with higher respiratory drive [33, 34]. Safe limits for driving pressure during assisted ventilation are not established yet, but its correlation with outcome in a small retrospective study supports using the same threshold used in controlled ventilation (<15 cmH₂O, the lower the better) [35]. Even if some expiratory muscle activity cannot be excluded in the presence of a flat plateau [36], this would cause an over estimation of the driving pressure, which, if anything, leads to set a safer rather than less safe ventilation.

ΔP_{occ} , the difference between PEEP and the lowest value of P_{aw} reached during an expiratory hold (described above as a way of predicting P_{mus}), can be used also to estimate the transpulmonary dynamic driving pressure. This maneuver is technically easier to perform than the inspiratory hold, because it does not require any post hold interpretation of the ventilator trace. An estimation of transpulmonary dynamic driving pressure can be made through a calculation from ΔP_{occ} :

Predicted Dynamic transpulmonary driving pressure = (Peak airway pressure – PEEP) – 2/3 ΔP_{occ} .

The AUROC for this predicted pressure to estimate an excessive dynamic transpulmonary driving pressure was >0.9 [21].

It is important to keep in mind that the measurement of plateau pressure and of ΔP_{occ} provide to the clinician complementary information, so measuring both of

them, especially in the absence of a Pes catheter, can allow a more complete description of the respiratory mechanics. Indeed, a recent study conducted in an experimental model of mild ARDS showed that a higher TV and DPaw, and not a higher dynamic driving pressure, were associated with worse lung and diaphragmatic injury [37].

6.3 Asynchronies

Asynchronies happen when the inspiratory and expiratory times of the patient and of the ventilator are partly or entirely not matched. Asynchronies are a common problem, affecting up to one-third of the patients [38], and a multicenter study (BEARDS, NCT03447288) specifically looking at the incidence of asynchronies during mechanical ventilation for ARDS is currently ongoing. Some studies showed an association between the incidence of asynchronies and outcomes (duration of mechanical ventilation, ICU mortality) [39–41]. While, on one side asynchronies might be a marker of more severe lung disease, and not a direct cause of worse outcomes, they can be associated with patient discomfort and cause an increase in the sedation administered [38]. It is important for the clinician at the bedside to recognize asynchronies when these happen and try to optimize the ventilator settings in order to reduce their incidence. Automated tools to recognize asynchronies and quantify their burden have been developed [42]. The most common asynchrony is ineffective triggering, occurring when the patient inspiratory effort fails to trigger the ventilator, because the pressure or flow generated by the muscles are not enough to overcome the trigger threshold. This can be a sign of muscle weakness or of the presence of intrinsic PEEP, which can be monitored either by Pes or Edi since, the presence of expiratory muscles activity does not allow to measure auto-PEEP through an expiratory hold during assisted ventilation. The decrease in Pes or the increase in Edi before the beginning of the inspiratory flow allow to estimate the amount of pressure that the inspiratory muscles have to overcome before being able to trigger the ventilator [27]. Another common asynchrony is double trigger or double cycling: this happens when the ventilator inspiratory time is shorter than the patient inspiratory time and the patient triggers another breath before a complete exhalation has happened [42]. It can cause the so-called breath stacking, meaning that the total tidal volume delivered is higher than intended and can lead to lung overdistension [43]. Lastly, auto-trigger is a breath delivered by the ventilator in the absence of patient's effort, triggered by cardiac oscillations or air leak. It can also lead to breath stacking. A more complete list of asynchronies can be found in [38]. The recognition of asynchronies is made easier in the presence of a Pes catheter or an Edi monitor. Both of them allow a direct visualization of the patient muscular activity, its intensity and its timing during the ventilator respiratory cycle [8–10]. In the absence of these monitors, the clinician should pay attention to the airway pressure and show waveforms on the ventilator, to identify the presence of asynchronies. Chapter 39 contains several images of asynchronies to allow the reader to familiarize more with this very common problem.

6.4 Distribution of Ventilation and Pendelluft

As already mentioned, Paw and Pes tracings allow a global monitoring of pressure distending the respiratory system, without discriminating between different regions. While normal lungs have a fluid-like behavior, with even distribution of the pressure generated by inspiratory muscles throughout the parenchyma, injured lungs show a “solid-like” behavior [44]. This means that some areas would not inflate and some other would be overdistrinded once exposed to the same distending pressure. As a consequence, a “pendelluft” phenomenon can develop as shown in Fig. 6.4. This is the movement of tidal volume inside the lung between zones with different time constants and it is not identified by the change in ventilator tracings nor by monitoring P_L . It can lead to regional overdistrindation of inflated lung regions [45, 46]. Electrical Impedance Tomography (EIT) is a bedside monitoring tool that allows to

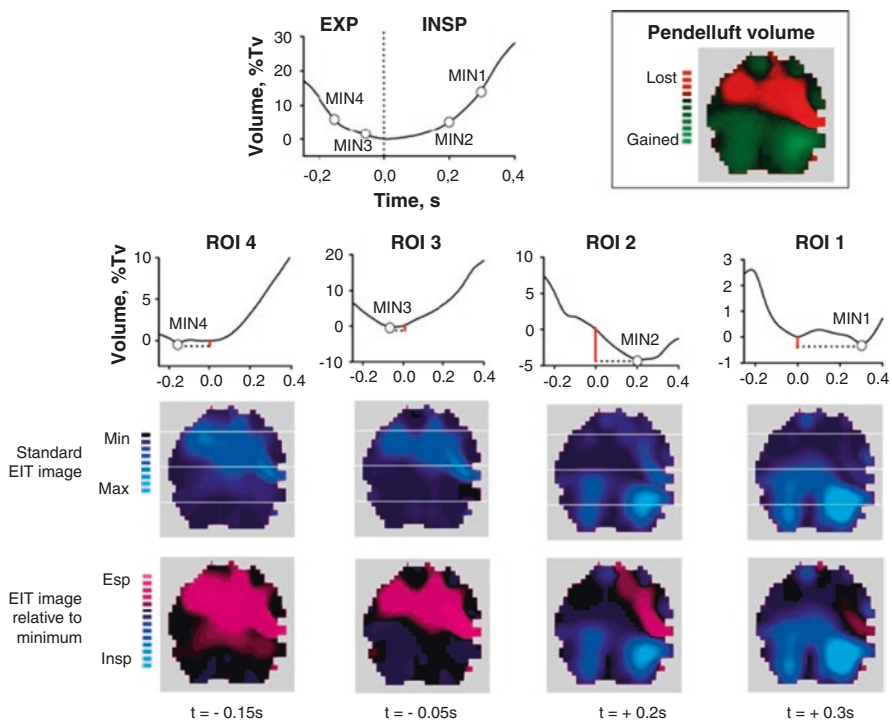


Fig. 6.4 Evidence of pendelluft in a patient during a weaning trial: dyssynchrony between different regions is noticed because of minimum impedance values (regional expiration) of the dorsal regions of interest (ROI 3 and 4) are reached during global expiration (EXP), while in the ventral ones (ROI 1 and 2) these are reached during inspiration (INSP). Hence, some gas volume (red bars) inflating ROI 3 and 4 came from the deflation of ROI 1 and 2: inspiration in the dorsal ROIs started when ventral ones were still expiring (expiration in purple color). Pendelluft gas moved from the ventral towards the dorsal lung regions (boxed image). (Reproduced under a Creative Commons Attribution 4.0 International License from [46])

visualize the differences in ventilation among different lung regions (see Chap. 33). EIT is the only monitor able to identify the presence of pendelluft phenomenon, visualized as the inflation of some lung regions while others are deflating [45]. This phenomenon was shown to increase with decreasing ventilatory support and is associated with ineffective ventilation and possible local overdistension [46]. Moreover, EIT may provide useful information in regard to changes in distribution of regional ventilation caused by breathing efforts [47].

6.5 Evaluation of Respiratory Muscles Activity by Ultrasound

Respiratory muscles ultrasound is a newer and rapidly evolving way to monitor the spontaneously breathing patients [48]. Diaphragm thickness and function have been extensively studied and also shown to correlate with outcome [2]. Taking advantage of the non-invasive and bedside availability of the technique, accessory inspiratory muscle and abdominal muscles have been the subject of more recent studies [49]. More details about respiratory muscles ultrasound are available in Chap. 32.

6.6 Conclusion

Several data, made available over the last decade, allow a better understanding of the benefits and risks inherent to allowing spontaneous breathing and the crucial role of patient's effort. In addition to esophageal pressure, several techniques are readily available at the bedside. A wider adoption of these in the clinical practice should proceed along with clinical research, defining the targets to prevent harm and improve patient's outcome.

References

1. Chanques G, Constantin JM, Devlin JW, Ely EW, Fraser GL, Gélinas C, et al. Analgesia and sedation in patients with ARDS. *Intensive Care Med.* 2020;46:2342–56. <https://doi.org/10.1007/s00134-020-06307-9>.
2. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. *Am J Respir Crit Care Med.* 2018;197:204–13. <https://doi.org/10.1164/rccm.201703-0536OC>.
3. Goligher EC, Brochard LJ, Reid WD, Fan E, Saarela O, Slutsky AS, et al. Diaphragmatic myotrauma: a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure. *Lancet Respir Med.* 2019;7:90–8. [https://doi.org/10.1016/S2213-2600\(18\)30366-7](https://doi.org/10.1016/S2213-2600(18)30366-7).
4. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med.* 2017;195:438–42. <https://doi.org/10.1164/rccm.201605-1081CP>.
5. Yoshida T, Fujino Y. Monitoring the patient for a safe assisted ventilation. *Curr Opin Crit Care.* 2021;27:1–5. <https://doi.org/10.1097/MCC.0000000000000788>.

6. Pinsky MR. Cardiopulmonary interactions: physiologic basis and clinical applications. *Ann Am Thorac Soc*. 2018;15:S45–8. <https://doi.org/10.1513/AnnalsATS.201704-339FR>.
7. Jubran A, Tobin M. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1997;155:906–15. <https://doi.org/10.1164/ajrccm.155.3.9117025>.
8. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, et al. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*. 2016;42:1360–73. <https://doi.org/10.1007/s00134-016-4400-x>.
9. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, et al. The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med*. 2014;189:520–31. <https://doi.org/10.1164/rccm.201312-2193CI>.
10. Pham T, Telias I, Beitler JR. Esophageal manometry. *Respir Care*. 2020;65:772–92. <https://doi.org/10.4187/respcare.07425>.
11. Bertoni M, Spadaro S, Goligher EC. Monitoring patient respiratory effort during mechanical ventilation: lung and diaphragm-protective ventilation. *Crit Care*. 2020;24:106. <https://doi.org/10.1186/s13054-020-2777-y>.
12. Tonelli R, Fantini R, Tabbi L, Castaniere I, Pisani L, Pellegrino MR, et al. Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in de novo respiratory failure: a pilot study. *Am J Respir Crit Care Med*. 2020;202:558–67. <https://doi.org/10.1164/rccm.201912-2512OC>.
13. Akoumianaki E, Vaporidi K, Georgopoulos D. The injurious effects of elevated or nonelevated respiratory rate during mechanical ventilation. *Am J Respir Crit Care Med*. 2019;199:149–57. <https://doi.org/10.1164/rccm.201804-0726CI>.
14. Costa R, Navalesi P, Cammarota G, Longhini F, Spinazzola G, Cipriani F, et al. Remifentanyl effects on respiratory drive and timing during pressure support ventilation and neurally adjusted ventilatory assist. *Respir Physiol Neurobiol*. 2017;244:10–6. <https://doi.org/10.1016/j.resp.2017.06.007>.
15. Laghi F, Karamchandani K, Tobin MJ. Influence of ventilator settings in determining respiratory frequency during mechanical ventilation. *Am J Respir Crit Care Med*. 1999;160:1766–70. <https://doi.org/10.1164/ajrccm.160.5.9810086>.
16. Pletsch-Assuncao R, Pereira MC, Ferreira JG, Cardenas LZ, De Albuquerque ALP, De Carvalho CRR, et al. Accuracy of invasive and noninvasive parameters for diagnosing ventilatory overassistance during pressure support ventilation. *Crit Care Med*. 2018;46:411–7. <https://doi.org/10.1097/CCM.0000000000002871>.
17. Yang KL, Tobin M. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med*. 1991;324:1445–50. <https://doi.org/10.1056/NEJM199105233242101>.
18. Karthika M, Al Enezi FA, Pillai LV, Arabi YM. Rapid shallow breathing index. *Ann Thorac Med*. 2016;11:167–76. <https://doi.org/10.4103/1817-1737.176876>.
19. Telias I, Damiani F, Brochard L. The airway occlusion pressure (P 0.1) to monitor respiratory drive during mechanical ventilation: increasing awareness of a not-so-new problem. *Intensive Care Med*. 2018;44:1532–5. <https://doi.org/10.1007/s00134-018-5045-8>.
20. Telias I, Junhasavasdikul D, Rittayamai N, Piquilloud L, Chen L, Ferguson ND, et al. Airway occlusion pressure as an estimate of respiratory drive and inspiratory effort during assisted ventilation. *Am J Respir Crit Care Med*. 2020;201:1086–98. <https://doi.org/10.1164/RCCM.201907-1425OC>.
21. Bertoni M, Telias I, Urner M, Long M, Del Sorbo L, Fan E, et al. A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. *Crit Care*. 2019;23:1–10. <https://doi.org/10.1186/s13054-019-2617-0>.
22. Pesenti A, Pelosi P, Foti G, D'Andrea L, Rossi N. An interrupter technique for measuring respiratory mechanics and the pressure generated by respiratory muscles during partial ventilatory support. *Chest*. 1992;102:918–23. <https://doi.org/10.1378/chest.102.3.918>.
23. Foti G, Cereda M, Banfi G, Pelosi P, Fumagalli R, Pesenti A. End-inspiratory airway occlusion: a method to assess the pressure developed by inspiratory muscles in patients with acute

- lung injury undergoing pressure support. *Am J Respir Crit Care Med.* 1997;156:1210–6. <https://doi.org/10.1164/ajrccm.156.4.96-02031>.
24. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med.* 1999;5:1433–6. <https://doi.org/10.1038/71012>.
 25. Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, et al. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. *Am J Respir Crit Care Med.* 2001;164:419–24. <https://doi.org/10.1164/ajrccm.164.3.2009018>.
 26. Colombo D, Cammarota G, Alemani M, Carezzo L, Barra FL, Vaschetto R, et al. Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. *Crit Care Med.* 2011;39:2452–7. <https://doi.org/10.1097/CCM.0b013e318225753c>.
 27. Bellani G, Coppadoro A, Patroniti N, Turella M, Marocco SA, Grasselli G, et al. Clinical assessment of auto-positive end-expiratory pressure by diaphragmatic electrical activity during pressure support and neurally adjusted ventilatory assist. *Anesthesiology.* 2014;121:563–71. <https://doi.org/10.1097/ALN.0000000000000371>.
 28. Mellado Artigas R, Damiani LF, Piraino T, Pham T, Chen L, Rauseo M, et al. Reverse triggering Dyssynchrony 24 h after initiation of mechanical ventilation. *Anesthesiology.* 2021;134:760–9. <https://doi.org/10.1097/ALN.0000000000000376>.
 29. Bellani G, Mauri T, Coppadoro A, Grasselli G, Patroniti N, Spadaro S, et al. Estimation of patient's inspiratory effort from the electrical activity of the diaphragm. *Crit Care Med.* 2013;41:1483–91. <https://doi.org/10.1097/CCM.0b013e31827caba0>.
 30. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. *Crit Care Med.* 2012;40:1578–85. <https://doi.org/10.1097/CCM.0b013e3182451c40>.
 31. Bellani G, Grasselli G, Teggia-Droghi M, Mauri T, Coppadoro A, Brochard L, et al. Do spontaneous and mechanical breathing have similar effects on average transpulmonary and alveolar pressure? A clinical crossover study. *Crit Care.* 2016;20:1–10. <https://doi.org/10.1186/s13054-016-1290-9>.
 32. Bellani G, Grassi A, Sosio S, Foti G. Plateau and driving pressure in the presence of spontaneous breathing. *Intensive Care Med.* 2019;45:97–8. <https://doi.org/10.1007/s00134-018-5311-9>.
 33. Sajjad H, Schmidt GA, Brower RG, Eberlein M. Can the plateau be higher than the peak pressure? *Ann Am Thorac Soc.* 2018;15:754–9. <https://doi.org/10.1513/AnnalsATS.201707-553CC>.
 34. Mezidi M, Guérin C. Complete assessment of respiratory mechanics during pressure support ventilation. *Intensive Care Med.* 2019;45:557–8. <https://doi.org/10.1007/s00134-018-5490-4>.
 35. Bellani G, Grassi A, Sosio S, Gatti S, Kavanagh BP, Pesenti A, et al. Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome. *Anesthesiology.* 2019;131:594–604. <https://doi.org/10.1097/ALN.0000000000002846>.
 36. Soundoulounaki S, Akoumianaki E, Kondili E, Padiaditis E, Prinianakis G, Vaporidi K, et al. Airway pressure morphology and respiratory muscle activity during end-inspiratory occlusions in pressure support ventilation. *Crit Care.* 2020;24:1–9. <https://doi.org/10.1186/s13054-020-03169-x>.
 37. Pinto EF, Santos RS, Antunes MA, Maia LA, Padilha GA, De Machado JA, et al. Static and dynamic transpulmonary driving pressures affect lung and diaphragm injury during pressure-controlled versus pressure-support ventilation in experimental mild lung injury in rats. *Anesthesiology.* 2020;132:307–20. <https://doi.org/10.1097/ALN.0000000000003060>.
 38. Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. *Mayo Clin Proc.* 2017;92:1382–400. <https://doi.org/10.1016/j.mayocp.2017.05.004>.
 39. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med.* 2015;41:633–41. <https://doi.org/10.1007/s00134-015-3692-6>.
 40. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med.* 2006;32:1515–22. <https://doi.org/10.1007/s00134-006-0301-8>.

41. Vaporidi K, Babalis D, Chytas A, Lilitsis E, Kondili E, Amargianitakis V, et al. Clusters of ineffective efforts during mechanical ventilation: impact on outcome. *Intensive Care Med.* 2017;43:184–91. <https://doi.org/10.1007/s00134-016-4593-z>.
42. de Haro C, Ochagavia A, López-Aguilar J, Fernandez-Gonzalo S, Navarra-Ventura G, Magrans R, et al. Patient-ventilator asynchronies during mechanical ventilation: current knowledge and research priorities. *Intensive Care Med Exp.* 2019;7:1–14. <https://doi.org/10.1186/s40635-019-0234-5>.
43. Beitler JR, Sands SA, Loring SH, Owens RL, Malhotra A, Spragg RG, et al. Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: the BREATHE criteria. *Intensive Care Med.* 2016;42:1427–36. <https://doi.org/10.1007/s00134-016-4423-3>.
44. Yoshida T, Fujino Y, Amato MBP, Kavanagh BP. Fifty years of research in ards spontaneous breathing during mechanical ventilation risks, mechanisms, and management. *Am J Respir Crit Care Med.* 2017;195:985–92. <https://doi.org/10.1164/rccm.201604-0748CP>.
45. Yoshida T, Torsani V, Gomes S, Santis RRD, Beraldo MA, Costa ELV, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med.* 2013;188:1420–7. <https://doi.org/10.1164/rccm.201303-0539OC>.
46. Coppadoro A, Grassi A, Giovannoni C, Rabboni F, Eronia N, Bronco A, et al. Occurrence of pendelluft under pressure support ventilation in patients who failed a spontaneous breathing trial: an observational study. *Ann Intensive Care.* 2020;10:39. <https://doi.org/10.1186/s13613-020-00654-y>.
47. Mauri T, Bellani G, Confalonieri A, Tagliabue P, Turella M, Coppadoro A, et al. Topographic distribution of tidal ventilation in acute respiratory distress syndrome: effects of positive end-expiratory pressure and pressure support. *Crit Care Med.* 2013;41:1664–73. <https://doi.org/10.1097/CCM.0b013e318287f6e7>.
48. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, et al. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients—a narrative review. *Intensive Care Med.* 2020;46:594–605. <https://doi.org/10.1007/s00134-019-05892-8>.
49. Schreiber AF, Sabatini U, Vorona S, Bertoni M, Piva S, Goligher E. Measuring abdominal muscle function by abdominal muscle thickening on ultrasound: reproducibility, validity and normal range values. *Eur Respir J.* 2019;54:OA5367. <https://doi.org/10.1183/13993003>.