The Impact of Mechanical Energy Assessment on Mechanical Ventilation: A Comprehensive Review and Practical Application

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Mechanical ventilation (MV) provides basic organ support for patients who have acute hypoxemic respiratory failure, with acute respiratory distress syndrome as the most severe form. The use of excessive ventilation forces can exacerbate the lung condition and lead to ventilator-induced lung injury (VILI); mechanical energy (ME) or power can characterize such forces applied during MV. The ME metric combines all MV parameters affecting the respiratory system (ie, lungs, chest, and airways) into a single value. Besides evaluating the overall ME, this parameter can be also related to patient-specific characteristics, such as lung compliance or patient weight, which can further improve the value of ME for characterizing the aggressiveness of lung ventilation. High ME is associated with poor outcomes and could be used as a prognostic parameter and indicator of the risk of VILI. ME is rarely determined in everyday practice because the calculations are complicated and based on multiple equations. Although low ME does not conclusively prevent the possibility of VILI (eg, due to the lung inhomogeneity and preexisting damage), individualization of MV settings considering ME appears to improve outcomes. This article aims to review the roles of bedside assessment of mechanical power, its relevance in mechanical ventilation, and its associations with treatment outcomes. In addition, we discuss methods for ME determination, aiming to propose the most suitable method for bedside application of the ME concept in everyday practice.

Keywords: **Respiration, Artificial**

Abbreviations: **ME** – mechanical energy; **MP** – mechanical power; **VILI** – ventilator-induced lung injury; **MV** – mechanical ventilation; **ARDS** – acute respiratory distress syndrome; **PPV** – positive pressure ventilation; **PBW** – cpredicted body weight; **DP** – driving pressure; **PEEP** – positive end-expiratory pressure; **RCT** – randomized controlled trial; **ECMO** – extracorporeal membrane oxygenation; **Vt** – tidal volume; **RR** – respiratory rate; **ICU** – Intensive Care Unit; **Ptp** – transpulmonary pressure; **WOBv** – work of breathing ventilator; **Pmean** – mean airway pressure; **FCV** – flow-controlled ventilation; **PSV** – pressure-support ventilation; **CT** – computed tomography

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/941287

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Background

Mechanical ventilation (MV) is used to provide basic organ support to patients who have acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) [1]. Gas exchange usually improves under the influence of positive pressure ventilation (PPV); however, the already-damaged lung parenchyma is affected by mechanical forces (energies) generated by PPV. These mechanical forces can worsen the underlying lung injury and cause ventilator-induced lung injury (VILI) [2]. Ventilator settings can, through forces exerted on the lungs by the ventilator, directly influence the development of VILI. For example, a 2000 study by the ARDS Network concluded that a reduction of tidal volume (Vt) to 6 ml/PBW (predicted body weight) had a significant effect on mortality in worldwide critical care [3]. Driving pressure (DP), which is the difference between positive end-expiratory pressure (PEEP) and plateau pressure), is relatively simple to set up in clinical practice, and its association with mortality has been demonstrated previously [4]. However, reducing DP as well as ventilation with a Vt of 6 ml/kg or less usually leads to hypercapnia. To reduce hypercapnia, most clinicians resort to increasing the respiratory rate (RR) [5]; this is, however, generally associated with an increase in mechanical energy (ME). The effect of additional parameters, such as Vt, DP, PEEP, plateau pressure, or flow, on the ventilator's contribution to lung injury is currently an important topic of research in the field of mechanical ventilation. Many parameters contribute to ventilator-induced lung injury (VILI) – there is growing evidence grows that these include RR [6], air flow[7], and strain [8,9]. The combined effect of these parameters represents the ME of ventilation. The effect of the ME generated by a PPV device on the respiratory system depends not only on the ventilatory settings, but also on the lung properties (eg, lung inhomogeneity, and lung size) [10]. Historically, ME measurements have been possible since the 1960s [11], but their use has not been implemented in everyday practice so far. ME seems to be a good prognostic marker, and high ME may indicate an increased risk of VILI development, but no randomized controlled trials (RCT) have defined clear cut-off limits of ME associated with VILI or mortality. Although associations between high ME and poor patient outcomes have been reported in many studies (see below), the fundamental question remains – is ME only a prognostic marker, or could it be used as a tool for the optimization and individualization of treatment?

Two characteristics are used to describe the energy applied to the respiratory system MV to exchange the alveolar gas. Mechanical power (MP) is the energy applied to the respiratory system of the patient by the ventilator per unit of time, typically a minute (ie, the cumulative inspiratory energy in joules per minute), while ME is the energy transferred to the lungs per individual breath by the ventilator [12]. It can be derived by integrating the curve characterizing the dependence of tidal volume on transpulmonary pressure [13].

Oxygenation and decarboxylation of hemoglobin and blood depend on factors such as alveolar perfusion and the ability to exchange the gases with blood. If the alveoli and the interstitium are severely damaged, extracorporeal membrane oxygenation (ECMO) should be considered instead of mechanical ventilation with high MP [14], and MP seems to be useful parameter for indication of ECMO [15]. The modern ME concept was first described by Gattinoni et al [16], who constructed an equation using individual ventilatory parameters for determining the total mechanical energy value (Eq. 2, presented in detail below). In addition, this equation also allows us to evaluate the effects of individual parameters on MP, showing that the Vt, DP, and inspiration flow increase ME exponentially with a growth factor of 2, while an increase in the positive end-expiratory pressure (PEEP) leads to a roughly linear increase in ME. ME also grows exponentially with the RR (growth factor of 1.4). Although this equation is relatively complicated for everyday use, it can be perceived as a guide for clinicians, telling them the degree to which individual parameters are associated with greater ME elevation, rather than as a tool for exact ME calculation [10].

No high-quality interventional trial showing that bedside measurement of ME improves patients' outcomes has been performed so far and further investigation is needed. This article aims to review the roles of bedside assessment of mechanical power and its relevance in mechanical ventilation. It also aims to provide clinicians with information necessary to introduce the ME concept into everyday clinical practice and presents current ME calculations facilitating bedside use. It summarizes the current algorithms for ME/MP calculation and discusses their clinical relevance and future directions of MP in critically ill patients.

It should be noted that various authors use various abbreviations for the same variables in their papers. For clarity, we unified these abbreviations in this paper and use the same abbreviations throughout the text.

MP as a Marker of Outcome

MP as a Predictor of Outcome in Animal and Preclinical Studies

An animal study by Araos et al indicated that histological lung injury and fibro-proliferation scores were positively correlated with MP [17]. Xie et al reported correlations of MP with serum transforming growth factor β1 (TGF-β1) and connective tissue growth factor (CTGF) (markers of fibrosis); the correlation coefficients were 0.424 and 0.581, respectively [18]. In a

retrospective analysis of patients undergoing open lung biopsy, Hsin-Hsien Li demonstrated that MP at ARDS diagnosis and ARDS duration before lung biopsy were independently associated with histological fibrosis [19]. MP was also associated with markers of VILI (C-X-C motif chemokine ligand 10/C-X-C Motif Chemokine Receptor 3) in an animal study by Xie Y et al [20].

ME as a Predictor of Outcome In Retrospective Clinical Studies

Fuller et al performed a retrospective analysis of 1705 mechanically ventilated patients in their Lung-Protective Ventilation Initiated in the Emergency Department trial (LOV-ED trial) [21]. Their study assessed clinical outcomes associated with the implementation of the early protocol of lung-protective mechanical ventilation. Although higher MP was shown to be independently significantly associated with a higher risk for ARDS development, the results were not too convincing (adjusted odds ratio (OR), 1.03 [1.00-1.06]).

In a study by Parhar et al, who analyzed a group of 731 ARDS patients, MP higher than 22 J/min in ARDS patients was associated with increased 28-day hospital mortality [22].

A retrospective analysis of a cohort of 306 children with ARDS from 55 pediatric intensive care units was performed by Bhalla et al [23], who found that higher MP was associated with a lower likelihood of being ventilator-free on day 28. Similarly, higher MP was associated with increased mortality in pediatric [24] and adult [25-31] ARDS patients, as well as in patients without ARDS [32,33].

A pooled database of 4549 patients with ARDS from 6 randomized clinical trials of protective mechanical ventilation and 1 large observational cohort of patients with ARDS was processed by Costa et al [34]. In their adjusted analyses, the DP, RR, and MP were significant predictors of mortality.

Urner et al analyzed the association between the intensity of dynamic MP and mortality [31]. They evaluated outcomes in patients with and without ARDS classified according to their DP (greater or lower than 15 cmH$_2$0) and MP (cut-off 17 J/minute). However, they only took the readings once a day at 8 AM. Despite this limitation, the authors concluded that both driving pressure and MP at the baseline were associated with a proportionally increased risk for Intensive Care Unit (ICU) mortality.

In the recent analysis by Senturk et al, the MP was assessed retrospectively from electronic recording systems [35]. In the 3042 patients, mortality in MP<11.3 J/min was 35.4%, and 49.1% in MP>11.3J/min. Mechanical ventilation days and ICU-length of stay were also significantly longer in the MP>11.3 J/min group. They used only a simple equation (No. 3 below) and concluded that the MP from the first 24 h was predictive for the ICU patients' prognosis.

Parameters of MV and ME as a Predictor of Mortality

The effect of lower and higher PEEP in ARDS patients with similar DP was described by Calvanti et al [36]. The 28-day mortality (all-cause mortality) was higher in the group with high PEEP, possibly due to the increased ME. In their retrospective analysis including 8207 patients, Serpa et al showed that higher ME was independently associated with higher in-hospital mortality in mechanically ventilated patients [37]. This was true even at low tidal volumes – MP higher than 17.0 J/min was independently associated with in-hospital mortality and increased risk of death. A similar study evaluating Vt based on ideal body weight found that even after normalization to the predicted body weight, the same Vt can generate different lung strains and different lung damage based on individual lung conditions [38]. A retrospective analysis of MP in COVID-19 (coronavirus disease 2019) and non-COVID-19 ARDS patients was performed in 1737 patients with almost 30% mortality [39]. The median MP during the first 24 h of ventilation was 19.3 [14.6-24.0] J/min in patients with and 13.2 [10.2-18.0] J/min in patients without COVID-19, and higher MP was associated with increased mortality independent of COVID-19. The authors considered only the first 24 h of MV to calculate the average MP.

Indexed ME (Normalized to Body Weight, etc.) for Mortality Prediction

Zhang et al investigated the reliability of ME for mortality prediction; the best results (especially in severe ARDS) were achieved with ME normalized to predicted body weight [40]. Some other authors also demonstrated an association of ME normalized to predicted body weight [41,42], even to lung capacity (specific power) [43] with mortality.

Methods of ME Calculation and its Bedside Use

ME and its Bedside Use

However, because of the calculation's complexity and specific limitations (see individual equations), MP calculation is nowadays rarely provided directly by ventilators, and bedside estimation of MP needs to be done manually based on ventilator-provided values supported by specifically measured parameters [44]. The complexity of lung disease and ventilator settings obviously do not allow ME to be used as the sole parameter. It appears that the best approach lies in the individualization of mechanical ventilation, taking ME into account as a summary parameter [45-57].
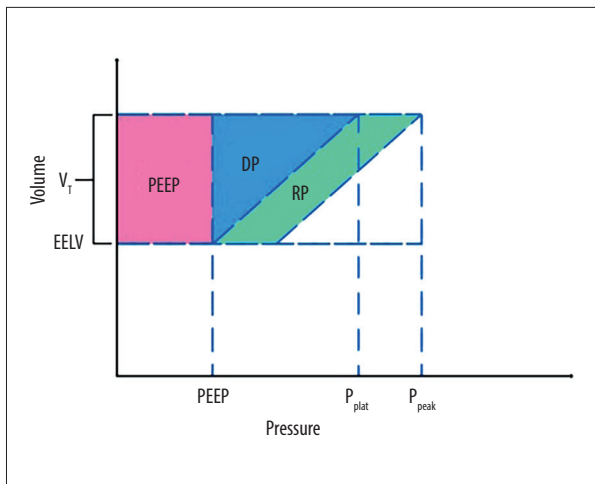
Figure 1. The geometrical method for calculating ME. Areas highlighted in color correspond to individual portions of ME. Pink – PEEP-related power. Blue – driving-pressure-related power. Green – resistive-pressure-related power. PEEP – positive end-expiratory pressure' DP – driving pressure; RP – resistive pressure; V_T – tidal volume; EELV – end-expiratory lung volume; P_{plat} – plateau pressure; P_{peak} – maximum pressure.

Unfortunately, the complexity of ME calculations and measurements limits their widespread use. The geometrical method has become the criterion standard in ME determination, but its bedside use is not practical [58]. Other methods using transpulmonary pressure (P_{tp}), which is difficult to measure accurately and is not widely monitored, have been proposed for both volume- and pressure-controlled ventilation. However, simplified equations have been derived from the original one to enable bedside calculations; individual methods along with their accuracy and limitations will be discussed below.

The Geometrical Method of Calculation

The geometrical method represents the criterion standard for determining ME as far as a physical measurement is concerned. It is presented in detail in **Figure 1** [58]. The energy of a single breath is described as the area under the pressure–volume ventilation curve [59]. The method assumes constant inspiration flow (square inspiration flow), the absence of spontaneous breathing, and a linear relationship between inspiration time and tidal volume, which increases during inspiration. In other words, the equation assumes constant values for respiratory system compliance and resistance during ventilation. If compliance changes during inspiration due to tidal recruitment, the method cannot yield accurate results. These relations were derived from the equation of motion (Eq. 1).

$$P_{peak} = DP + PR + PEEP \qquad (1),$$

where P_{peak} is the peak airway pressure, DP is the elastic pressure or driving pressure that overcomes the elastic recoil of alveoli, PR is the resistive pressure that overcomes airway resistance, and PEEP is the positive end-expiratory pressure.

The geometrical method has been used in the experimental animal model of VILI using P_{tp} by Cressoni et al [60]. In their study, both controlled and assisted ventilation regimens were used. Unit conversion to J/min was achieved by multiplying the area under the curve by a conversion constant of 0.098 and the respiration frequency (RR). In their experiment, various combinations of MV settings were tested. MP above approximately 12 J/min (MP applied to the lung expressed using P_{tp}) led to the development of whole lung edema. The authors reported a significant relationship between ME and lung elastance (r^2=0.33, P<0.01) as well as a negative relationship between PaO$_2$/FIO$_2$ (Partial Pressure of Oxygen/Fraction of Inspired Oxygen) (r^2=0.40, P<0.001).

ME in Volume-Controlled Ventilation

The original equation for ME in volume-controlled ventilation (Eq. (2), derived by Gatinnoni et al, implements Vt, RR, resistance, elastance, and inspiration time [16].

$$ME = RR \cdot \left\{ Vt^2 \cdot \left[\frac{1}{2} \cdot EL_{rs} + RR \cdot \frac{(1+I:E)}{60 \cdot I:E} \cdot R_{aw} \right] + Vt \cdot PEEP \right\} \qquad (2),$$

Where RR is the respiratory rate, EL_{rs} is the elastance of the respiratory system, Vt is the tidal volume, PEEP is the positive end-expiratory pressure, and I: E is the inspiratory-to-expiratory ratio.

To acquire the numerical values, it is necessary to perform an inspiration-hold maneuver. The equation takes into account both the flow resistance and the elasticity of the respiratory system, but it assumes a linear change in compliance during a breath (in a given range of pressures/volumes). Constant resistance and inspiration flow were also assumed during inspiration. Overall, this formula leads to an underestimation of ME compared to the geometrical method (albeit clinically negligible, below 10%) [61]. Moreover, the equation complexity limits its bedside use.

Wu et al compared the Gattinoni's equation (Eq. 2) with MP measured by integration of the areas within the pressure–volume loops [62] in 25 invasively ventilated patients, arguing that Gattinoni's equation is influenced by PEEP (which theoretically does not contribute to MP) and, therefore, is not accurate. The correlation btween MP obtained using their method and Eq 2 was relatively low, with R^2 of 0.75 and 0.66 at PEEP values of 5 and 10 cmH2O, respectively. Hence, the authors concluded that PEEP does not produce net displacement or contribute to MP, which is in opposition to many authors [16,63].

Their conclusion is, however, questionable – if excluding PEEP from their geometrical method, it is logical that the correlation with an equation agreeing well with the geometrical method that includes PEEP will be low.

The same team who derived the Eq. (2) simplified it and derived Eq. (3) using P_{peak} (peak inspiratory pressure, maximum end-expiratory pressure), P_{plat} (plateau pressure), Vt, RR, and PEEP.

$$MP = 0.098 \cdot RR \cdot V_t \cdot \left[P_{peak} - \frac{1}{2} \cdot \left(P_{plat} - PEEP \right) \right] \quad (3),$$

where RR is the respiratory rate, Vt is the tidal volume, P_{peak} is the maximum inspiration pressure, PEEP is the positive end-expiratory pressure and P_{plat} is plateau pressure.

The derived equation and geometrical method correlated well, with the bias between the geometric method and Eq. 3 being 0.053 (-0.81; 0.77) J/min and -0.4 (-1.50; 0.70) J/min at the inspiration flows of 30 L/min and 60 L/min, respectively (r^2=0.96 and 0.97, P<0.01) [64]. At higher flows, however, the tissue resistance should be considered in addition to the physiological increase in the respiratory tract resistance. Still, it is necessary to keep in mind that if the high flow is caused by increased resistance of the endotracheal tube, the increase in ME is used to overcome the endotracheal tube resistance and, in effect, does not affect the lung and the incidence of VILI, respectively. On the other hand, impairment of lung mechanics leads to an increase in ME, which definitely contributes to VILI development [8].

Essentially the same equation (Eq. 4; originally without a constant 0.098 for correction to J/min) was proposed by Louis et al [61]

$$MP = RR \cdot Vt \cdot \left[\frac{PEEP}{2} - \frac{P_{plat}}{2} + P_{peak} \right] \quad (4,)$$

where RR is the respiratory rate, Vt is the tidal volume, P_{peak} is the maximum inspiration pressure, P_{plat} is the plateau pressure, and PEEP is the positive end-expiratory pressure.

The geometrical method and both the original and simplified equations were compared in supinated and pronated patients with ARDS by Louis et al [61]. A good correlation was demonstrated with the absolute value of difference not exceeding 8.3%, which corresponds to a difference of approximately 2 J/min.

Giosa et al proposed another simplified equation not necessitating the inspiration-hold maneuver (Eq. 5) [65]. This equation is more suitable for bedside use; unfortunately, this comes at the cost of a decrease in calculation accuracy. Resistance in the equation is replaced by a constant value of 10 cmH$_2$O/L/s, which well-matches most intubated patients. However, the more the actual resistance exceeds the value of 10, the more inaccurate the calculation will be. The equation underestimates ME in higher inspiration flows, where the respiratory tract resistance can be significantly increased by the occurrence of turbulent flow. Nevertheless, the calculated error is clinically negligible up to a value of 15 cmH$_2$O/L/s, and the mean difference between the 2 methods of calculation at resistances of 20 cmH$_2$O/L/s is approx.1.3 J/min [65]. The deviation associated with the use of Equation 5 from the geometrical method, ie, -0.0074 (-0.93;0.91) and -1.0 (-2.52;0.45) J/min for flows of 30 and 60 l/min, respectively, was acceptable [64].

$$ME = \frac{Vt \cdot (P_{peak} + PEEP + F/6)}{20} \quad (5),$$

where Vt is the tidal volume, P_{peak} is the maximum inspiration pressure, PEEP is the positive end-expiratory pressure, and F is the inspiratory flow.

All equations shown above assume volume-controlled ventilation, absence of spontaneous breathing, and constant inspiration flow. Also, the respiratory system was considered homogeneous, but in clinical practice, lungs are usually heterogeneous due to lung inhomogeneities (especially in ARDS patients) [66], which means that even in the same patient, the same ME could be safe or damaging in different lung regions. However, despite the described simplifications, the equations correlate well with the geometrical method, the maximum calculation difference being 2 J/min. From this perspective, it would be logical to use methods of calculation not necessitating the inspiration-hold maneuver in clinical practice (Eq. 5).

Aşar et al describe a method using the Work of Breathing ventilator (WOBv) parameter [67] measured by some ventilators. WOBv is the amount of energy consumed to ventilate 1 liter of gas, and the unit is expressed as J/L. By multiplying WOBv with RR, we get work per unit of time (i.e., the power) [68]. Taking PEEP into account, Aşar et al derived an equation of dynamical mechanical power (MP$_{dyn}$) (Eq. 6).

$$MPdyn = (WOBv \cdot MVe) + (0.098 \cdot PEEP \cdot MVe) \quad (6),$$

where MVe is the expiratory minute volume.

The authors compared this equation with that formulated by Gattinonis (Eq. 2) in 40 adult ARDS patients with volume-controlled ventilation and deep sedation. Both equations correlated well with $R^2 \geq 0.98$.

Chi et al proposed a simple formula including mean airway pressure (P_{mean}) [69] and tested it in the volume-controlled ventilation mode with a constant inspiratory flow and without inspiration-hold maneuver (Eq. 7).

$$MP = (0.1 \cdot MV \cdot (Pmean + (Pmean - PEEP) \cdot E:I) \quad (7),$$

where MV is the minute ventilation in L/min, P_{mean} is the mean airway pressure, PEEP is the positive end-expiratory pressure, and E: I the expiratory: inspiratory ratio

The formula was also validated against that by Gatitinonis (Eq. 2) in 50 ARDS and 50 non-ARDS patients using T_{plat} settings of 0 and 0.5 s. At both T_{plat} levels, the P_{mean}-derived MP correlated very well with the reference MP both in patients with or without ARDS. The equation also implies that providing that MV, PEEP and I: E (the inspiratory: expiratory ratio) settings are stable, the P_{mean} alone could reflect the dynamic changes of MP, which could be easily monitored by clinicians. The same authors suggest in their retrospective analysis that patients with elevated P_{mean} during the first 24 h of mechanical ventilation had worse outcomes, even if a low tidal volume strategy was applied [70]. P_{mean} was recognized as an independent risk factor for poor outcomes, with an odds ratio of 1.35 (95% CI 1.29-1.42).

ME in Pressure-Controlled Ventilation

In pressure-controlled ventilation, where the pressure in the respiratory tract remains constant and the flow decreases during ventilation (which is also associated with the decreased airway resistance and non-linear pressure–volume relationship), the Van Der Meijden equation can be used (Eq. 8) [71,72]. Besides Vt and RR, this equation also takes into account the respiratory system compliance and resistance, PEEP, DP, and T_{insp} (inspiration time).

$$ ME = 0.098 \cdot RR \cdot V_t \cdot \left[PEEP + DP \cdot \left(1 - e^{\frac{-T_{insp}}{R \cdot C}}\right) \right] \quad (8), $$

where RR is the respiratory rate, Vt is the tidal volume, PEEP is the end-expiratory pressure, DP is the driving pressure, T_{insp} is the inspiration time, R is the resistance, and C is the compliance.

Compliance and resistance calculations are based on volume-controlled ventilation with a constant inspiratory flow of 30 L/min during the end-expiratory and end-inspiratory pauses. This equation assumes constant airway resistance during inspiration. However, the airway resistance is a function of the airflow and changes during inspiration, which reduces the accuracy of results obtained using this equation. However, the correlation of these results with the geometrical method was very good (mean difference of -0.001 J/min, with the upper and lower limits of agreement being 2.05 and -2.05 J/min, respectively) [64]. A simplified version of the same equation was proposed by Becher [73] (Eq. (9)):

$$ ME = 0.098 \cdot RR \cdot V_t \cdot [PEEP + DP] \quad (9), $$

where RR is the respiratory rate, Vt is the tidal volume, PEEP is the end-expiratory pressure, and DP is the driving pressure.

This simplification is based on the assumption that the pressure wave is ideally squared. Despite this significant simplification, this equation still correlated well with the geometrical method (r^2=0.94, p<0.001) with a bias of -0.81 J/min, and with the upper and lower limits of agreement of 2.11 and -0.48 [64]. When compared with the original equation by Van Der Meijden, it performed well, with an even narrower confidence interval. Therefore, Chiumello et al concluded that the simplified version (Eq. 9) seems to better fit the need for bedside ME calculations than Eq. 8, even in terms of precision [64]. On the other hand, Van Der Meijden claimed that the Becher's equation (Eq. 9) was less accurate than the original Equation 8 (limits of agreement 8.6% vs 13%) [71].

If the inspiratory pressure rise time is considered, the equation becomes more complex (Eq. (10)) [73]:

$$ ME_{PCV(slope)} = 0.098 \cdot RR \cdot \left[(DP + PEEP) \cdot V_t - \Delta P_{insp}^2 \cdot C \cdot \left(0.5 - \frac{R \cdot C}{T_{slope}} + \left(\frac{R \cdot C}{T_{slope}}\right)^2 \cdot \left(1 - e^{\frac{-T_{slope}}{R \cdot C}}\right) \right) \right] (10), $$

where RR is the respiratory rate, Vt is the tidal volume, PEEP is the end-expiratory pressure, DP is the driving pressure, R is the resistance, C is the compliance, and T_{slope} is the inspiration rise time.

Becher further compared the geometric method with the simplified equation (Eq. 9) they previously proposed and with the equation considering T_{slope} (Eq. 10) in a group of 42 patients [73]. The ME determined by the geometrical method was highly correlated with the results of both equations (Eq. 9 and 10). These results have shown that in bedside practice, T_{slope} is not as crucial and can be neglected.

Guérin et al described the influence of DP on patient mortality in a retrospective analysis of patients with ARDS in 2 RCT trials – the Acurasys [74] and Proseva [75] studies [76]. Patient mortality was lower if the ME during the first day of ventilation was ≤12 J/min, although the difference was not reported, likely not being too high (although it was statistically significant). However, they only evaluated the effect of ME on the first day of ventilation and not over the entire course of the treatment, which can be considered a limitation of that study. Moreover, they calculated ME using a greatly simplified equation (Eq. 11), which mainly considers the DP effect on ME.

$$ ME = 0.098 \cdot V_t \cdot RR \cdot DP \quad (11), $$

where RR is the respiratory rate, Vt is the tidal volume, and DP is the driving pressure. This is essentially the same equation as Eq. (9), but does not consider PEEP. As PEEP in their study was not significantly different between the groups, this may be fine for the findings of their study; however, taking this into consideration is important when discussing the threshold of 12 J/min, as including the mean PEEP found in their study into

the equation and calculating ME according to the Eq. (9), the applied ME would almost double.

ME in Flow-Controlled Ventilation (FCV)

Flow-controlled ventilation is a ventilatory mode where both inspiratory and expiratory flow rates are maintained at a constant level by regulating tracheal pressure, whereas tidal volume and respiratory rate vary depending on ventilator settings [77]. In a study with 10 ARDS patients, Grasseto et al reported reduced MP in FCV compared to volume-controlled ventilation as a consequence of lower inspiratory flow rates and breathing frequencies, which potentially reduces the dissipated energy [78]. However, they did not specify the method of MP measurement.

ME in Pressure-Support Ventilation (PSV)

All the abovementioned algorithms assume fully controlled ventilation without any spontaneous ventilation effort by the patient; therefore, these methods of mechanical energy determination can only be applied to patients who are sedated or even are on myorelaxation. Calculations of ME are more complicated in the case of PSV because the patient's lung is stretched not only by the ventilator-generated pressure but also by the patient's spontaneous effort. The pressure inflating the lung, therefore, is the sum of pressures generated by the ventilator and by the patient. It is impossible to easily measure the overall pressure and lung compliance, which necessitates the use of an esophageal catheter for P_{tp} measurement. If P_{tp} is not used and ME is calculated only on the basis of the ventilator-provided pressure values, ME could be significantly underestimated. To acquire the correct ME, the P_{tp} must be known and the calculation must be performed using the geometrical method. Spontaneously ventilating patients can be subjected to excessive ME and P_{tp}, putting them at risk of lung damage [79]. This phenomenon is called self-inflicted lung injury (SILI) and can influence treatment outcomes [80].

ME Thresholds Increasing VILI Probability

Cut-off values indicating an increased risk of VILI development have been proposed, but evidence for their clinical relevance is not strong and more human studies are needed to confirm these values. Moreover, much of the available data originate from animal models. The clinical relevance of such data to real-world ARDS patients is questionable, as these studies used healthy animals ventilated extremely aggressively. It is also important to distinguish P_{tp}-calculated ME (mechanical energy of the lung, ME_{lung}) from ME calculated for the whole respiratory system (ME_{rs}, ie, including lungs, airways, and thoracic wall).

Saffaran et al investigated the effect of multiple ventilation settings on reducing ME and DP, aiming to determine whether it is possible to minimize DP and ME while preserving gas exchange and respiratory rate [81]. They succeeded in reducing ME and DP in 66% and 23% of adults, respectively. Kassis et al applied predictive modeling to estimate the effects of modifying ventilator parameters on DP and MP in 2622 ARDS patients from the Medical Information Mart for Intensive Care IV database [82]. Reducing V_T led to a decrease in DP and MP, with a more pronounced effect on MP in patients with lower lung compliance. On the other hand, strategies reducing RR consistently increased MP. This is not surprising when looking at Eq. (2), as RR is associated with MP with a growth factor of 1.4, but V_T needed to be adjusted to maintain the minute ventilation, with a growth factor of 2. Rietveld et al investigated MP in volume-controlled and pressure-controlled ventilation with different pause times (T_{plat}) in 46 patients, finding that volume-controlled ventilation without pauses yielded the lowest MP [83]. Romitti et al ventilated healthy pigs for 48 h at MP of 3, 7, or 12 J/min [84]. Mechanical ventilation increased the lung weight, and worsened the lung histology, regardless of the ME. ME measurements using various ventilation settings were tested on healthy pigs by Cressoni et al using a geometrical method and P_{tp} [60]. For 54 h, healthy piglets were ventilated with identical constant high transpulmonary pressure and tidal volume, but the respiratory rate was set differently in individual groups. Ventilator setups with ME_{lung} greater than 12 J/min lead to VILI development (based on computed tomography scans). To further confirm this finding, the authors applied a low tidal volume with a high respiratory rate to reach a power greater than 12 J/min. This led to VILI development in all piglets in this group. Further, the influence of the inspiratory flow was investigated by adjusting the inspiratory-to-expiratory ratio. A higher flow was associated with VILI, which may be explained by the fact that under the same tidal volume, a shorter inspiratory time means a higher airway pressure, corresponding to a higher ME [8].

MP thresholds for VILI were tested in the aforementioned study by Guérin et al [76], whose threshold of 12 J/min, however, did not consider PEEP. Besides, only the initial MP on day 1 was considered and although the difference was significant, the degree of association (hazard ratio) between the groups with initial MP below and above that threshold was not reported.

Another retrospective observational study with a large cohort by Serpa et al showed an increase in the risk of death with ME_{rs} greater than 17 J/min [37]. Santer et al investigated ME during general anesthesia in a retrospective study of 230 767 elective, noncardiac adult surgical out- and inpatients whose MP was monitored [85]. The median intraoperative MP was 6.63 (interquartile range of 4.62 to 9.11) J/min and MP was higher in patients with postoperative respiratory failure compared to those without failure (adjusted odds ratio of 1.31 per 5 J/min

increase; 95% CI, 1.21 to 1.42; $P<0.001$). Of course, an association does not mean that there is a causal relationship (patients who were ventilated with high MP might have been in a generally worse condition than those in whom low MP was sufficient).

VILI itself is caused by the energy delivered to the lung parenchyma (ME_{lung}). However, this is only a portion of the total ME_{rs} and to be able to extract the pulmonary part of ME only, P_{tp} must be monitored. The relationship between ME_{rs} and ME_{lung} is usually linear, and separate thresholds for VILI incidence were established for ME_{lung} and ME_{rs} by Cressoni in an animal model [86]. These data cannot, however, be directly used in patients, and further investigation is needed.

Dianti et al described the effects of multiple parameters, including MP, on mortality in 9 trials comprising 4731 subjects, concluding that increased V_T, DP, and MP were associated with increased mortality [87]. In a prospective study on 51 adults with moderate-to-severe ARDS, Haudebourg et al described the effect of a DP-guided (DP between 12 and 14 cm H_2O) versus PBW (predicted body weight)-guided (6 ml/kg PBW) ventilation on MP [88]. DP-guided ventilation led to an increase of Vt from 6.1 mL/kg PBW [5.9-6.2] to 7.7 ml/kg PBW [6.2-8.7], and to a significant decrease in MP from 31.5 J/min [28-35.7] to 28.8 J/min [24.6-32.6] ($P<0.001$), representing a relative decrease of 7%. The MP values initially appear to be relatively high, but they used a different equation in their calculations.

Although ME itself can provide valuable insight into the risk of VILI development, it cannot be perceived as an isolated parameter [89-91]. Rather, it should be understood as a complex sum of many factors, the mutual relationships of which need to be taken into account. For example, reducing PEEP in an effort to decrease ME could lead to lung collapse, which would impair lung compliance and, in effect, a higher DP would be needed to achieve the same Vt. This could, in effect, lead to the exact opposite result than the original intention, ie, an increase in ME. It is, therefore, reasonable to increase PEEP and titrate ventilatory settings to achieve the best combination of given parameters providing the best trade-off between satisfactory gas exchange and safe ME.

The ME concept has also other pitfalls and limitations [90]. The assumption of a linear relationship between ME and PEEP used in most equations could be mathematically incorrect. MP, as defined today, relates to the inspiratory phase only, although the expiratory phase may also play a role in the development of VILI [92].

ME Effects on Lung Parenchyma

It is important to note that the negative influence is only exerted by the portion of ME affecting lung parenchyma, while the portion affecting the endotracheal tube does not influence VILI development. Preexisting lung parenchyma condition is another important factor in the risk for VILI occurrence. Lungs with strong heterogeneous impairment or a small area that can be ventilated will, upon absorption of ME, suffer greater damage than a homogeneous lung with normal physiological volume [66]. Lung injury depends on the mass of the lung absorbing ME [40] and on the energy "intensity" affecting the ventilated lung area [93]. It must, therefore, be considered that high Vt in itself is not necessarily injurious and the ME concept could help distinguish hazardous ventilation from safe ventilation even at high V_T [94]. This might explain why the outcomes of patients without ARDS (ie, those with a high functional residual capacity and high total lung volume) ventilated with high Vt (10 mL/kg) were not worse than those in patients ventilated with 6 mL/kg [95].

Future Directions

The ME concept summarizes the effects of multiple parameters on the total load on the lung parenchyma by the ventilator. So far, no high-quality RCTs have tested ME as a key parameter for VILI development or mortality rate. In the future, such a study is needed so that ME can be taken as a strong parameter for clinical practice. When using ME in clinical practice, one should be aware of limitations of the particular equation used and consider it in the implications for treatment. ME could be used to evaluate the overall effect of mechanical ventilation and to help set the ventilator parameters to reduce the risk of VILI. For this purpose, physicians should aim to ensure sufficient gas exchange with the lowest possible ME. The absolute numerical value of ME alone, however, may not produce sufficiently precise information to always guide safe ventilatory practice, and patient-specific parameters should be also taken into account [96]. If the usefulness of the ME concept is supported by sufficiently strong data, ME could be calculated using, eg, mobile apps; even better, it could be easily incorporated into the software of mechanical ventilators.

Conclusions

Simplified equations show promise and could be suitable for use in pressure-controlled and volume-controlled ventilation settings. The decrease in calculation accuracy caused by such simplification was shown to be low enough not to limit bedside use in everyday practice, as it does not outweigh the practicability of being easily able to calculate ME at the bedside using a mobile phone or handheld calculator [61,97]. For volume-controlled ventilation, the equation by Giosa et al (Eq. 5) could be used with good accuracy while avoiding the necessity of the inspiration-hold maneuver. For pressure-controlled

ventilation, the very simple equation by Becher et al (Eq. 9) could be used with satisfactory accuracy. The equations assume fully controlled ventilation without spontaneity. Continual ME measurement by a dedicated calculator or device that could use a more complex equation (or calculate ME according to the geometric method in real time) would possibly yield even better results and has been even implemented in some ventilators [98]. However, the degree of clinical improvement when using continuous monitoring and the clinical relevance of using such a more complex method have yet to be established.

Declaration of Figure's Authenticity

The figure submitted was created by author TE, who confirms that the image is original with no duplication and has not been previously published in whole or in part.

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