Impact of Humidification Strategy During Lung (and Heart)-Protective Ventilation

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8.1 Lung-Protective Ventilation Is Not Only Tidal Volume Reduction

Lung-protective ventilation (LPV) strategies refer to the ventilator settings that allow a protection of the lungs from injuries related to high volumes and consequently high alveolar and transpulmonary pressures that occur during invasive mechanical ventilation [1]. Lung-protective ventilation proved benefits on mortality and is recommended in ARDS patients [2–5] and in patients without ARDS [6–8]. The first component of LPV is the reduction of the tidal volume, but this is not the only parameter involved in LPV. There are other important ventilator settings to consider as well as airway management to optimize.

To ensure adequate carbon dioxide removal, the reduction in tidal volume should be associated with increasing of the respiratory rate. The tidal volumes have progressively been decreased over time in the operating room and in critically ill patients [9]. Similarly, respiratory rates have been progressively increased, up to 30–35 breath/min in most severe patients [10], and low or very low tidal volumes (below 6 ml/kg PBW) must be associated with high or very high respiratory rates (25 breaths/min or even higher) (Fig. 8.1). In those situations, the impact of dead space on CO_2 removal is critical [10].

FiO_2 and positive end-expiratory pressure (PEEP) settings are mainly focusing on oxygenation control but may also have an impact on CO_2 removal. High PEEP levels and low compliance may lead to alveolar distention and alveolar capillaries compression that may be responsible for an increase in alveolar dead space, a

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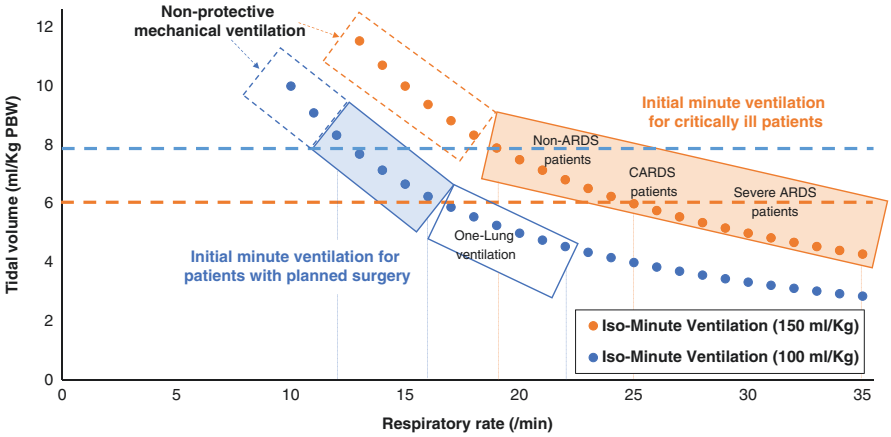

Fig. 8.1 This figure is a schematic representation of the findings based on the analysis of more than 30 studies providing respiratory rate and tidal volumes in different settings (intensive care units and operating room) for more than 40,000 patients [10]. Usual respiratory rates and tidal volumes are represented for surgical patients (planned surgery and one-lung surgery with protective ventilation) and critically ill patients (non-ARDS, ARDS with protective and ultra-protective ventilation and CARDS (COVID-19 ARDS) patients). The targeted minute ventilations are very different as well as the tidal volume and respiratory rate based on the category of patients. **In the operating room for planned surgery,** the patient's metabolism is usually low, and the body temperature is frequently below or equal to 36 °C. The CO_2 production is therefore low, and minute ventilation around 100 ml/kg/min PBW as shown by Radford in 1955 and used for a long time, is still adequate [10, 44, 67]. In addition, the recommended target tidal volume has progressively been reduced and is now around 8 ml/kg PBW or below; consequently, respiratory rate should be set between 12 and 16 breaths/min. In patients with one-lung ventilation (targeted tidal volume 4–6 ml/kg PBW), the respiratory rate should be set between 16 and 22 breaths/min. **In critically ill patients**, the metabolism is high and body temperature may be elevated. The CO_2 production is high, the dead space is high (including instrumental dead space), and ventilation needs to allow CO_2 elimination are higher than normal. In our study, we showed that in mechanically ventilated patients in ICU, minute ventilation was around 150 ml/kg/min PBW (25 studies conducted in ICUs) [10]. The respiratory rate must be frequently set above 20 breaths/min in critically ill patients. It is logical to use high respiratory rate after intubation of septic patients (with pneumonia or other cause of SIRS) breathing above 30/min before intubation. Some patients are ventilated after intubation with both reduced tidal volume and low respiratory rates (15 or below), which can result in severe acidosis

marker of ARDS severity [11, 12]. High FiO_2, when associated with hyperoxaemia, will be responsible for the Haldane effect, the reduction in haemoglobin affinity for CO_2 leading to increased $PaCO_2$ [13]. PEEP and FiO_2 settings are part of LPV and may have a role to explain severe hypercapnia during LPV but will not be discussed here.

The other frequently overlooked parameter involved in the CO_2 control is the total dead space that is part of the formula of the alveolar ventilation (Valv) that

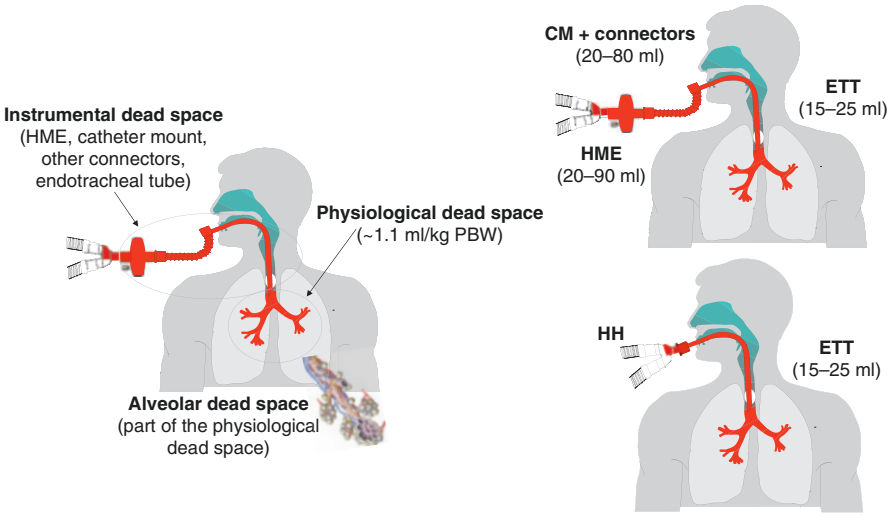

Fig. 8.2 Different portions of the dead space in the intubated patient. Dead space may be divided into instrumental dead space and physiological dead space (including airway and alveolar dead space). Part of the instrumental dead space may be easily limited by reducing the number of useless connections and by using a heated humidifier instead of a heat and moisture exchanger (HME) for gas humidification. Part of the instrumental dead space is not easily reduced: the endotracheal tube (ETT) may be changed for a tracheostomy tube to reduce the dead space by 10–12 ml, or ETT may be cut but the gain is very limited (2–4 ml)

reflects the part of the effective ventilation for CO_2 clearance. Noteworthy, dead space is frequently described as physiological and alveolar dead space, and instrumental dead space is usually neglected [14, 15], while it may represent the main dead space volume [16, 17].

The different parts of the total dead space (alveolar dead space, anatomic dead space and instrumental dead space) must be known to optimize mechanical ventilation during lung-protective ventilation (Fig. 8.2) [18]. This is particularly true in most severe patients when tidal volumes are low or very low and respiratory rate is high (Fig. 8.1). Consequently, the humidification strategy is critical through the limitation of instrumental dead space that is mainly related to connectors after the Y-piece and frequently to heat and moisture exchangers [18–20]. The current management in most ICU patients with or without ARDS must include lung-protective ventilation and should also incorporate heart-protective ventilation with optimization of CO_2 removal (Fig. 8.3).

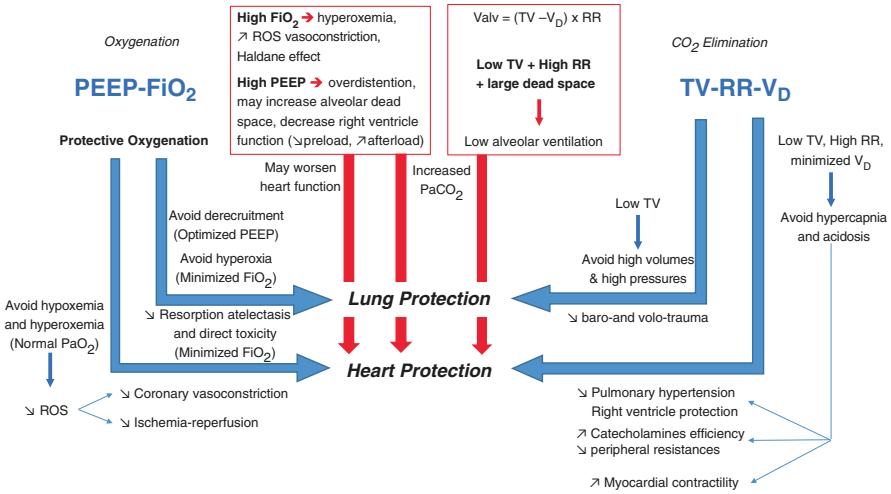

Fig. 8.3 Concept of heart- and lung-protective mechanical ventilation. Respiratory parameters to manage oxygenation (PEEP, FiO_2) and the parameters involved in carbon dioxide clearance (tidal volume (TV), respiratory rate (RR) and total dead space (VD)) may all have an impact both on lung and heart protection by different mechanisms. *PEEP* positive end-expiratory pressure, *FiO*$_2$ fraction of inspired oxygen, *TV* tidal volume, *RR* respiratory rate, *VD* total dead space, *Valv* alveolar ventilation, *ROS* reactive oxygen species

8.2 From Lung-Protective Ventilation to Lung- and Heart-Protective Ventilation

The concept of heart-protective ventilation, and especially right ventricle-protective ventilation, is derived from an abundant literature that describes the impact of mechanical ventilation, acidosis and hypercapnia on heart function [21] (Fig. 8.3). There was a gradual shift from tolerance of severe acidosis associated with promotion of lung-protective ventilation and "permissive hypercapnia" to more cautious management and recommendations to avoid severe respiratory acidosis, especially in the case of right ventricular dysfunction.

While "permissive hypercapnia" has been the first name of lung-protective ventilation [22, 23], high levels of hypercapnia have been accepted and encouraged with associated respiratory or mixed acidosis in ICU patients [24]. In addition to the beneficial impact of reduced tidal volumes, hypercapnia could have additional benefits in experimental studies [25]. The questions regarding the haemodynamic impact of metabolic and respiratory acidosis have been debated for a long time [26–28]. Although hypercapnic acidosis reduces myocardial contractility and reduces the effect of epinephrine on contractility [26] and reduces systemic vascular resistance [29–31], the net impact of hypercapnia is an increase in cardiac output [28, 31] through sympatho-adrenal mechanisms. Oxygen delivery is further increased in hypercapnic acidosis as a result of a rightward shift in the oxyhaemoglobin dissociation curve [32].

However, recent data have highlighted the deleterious effects of excessively high $PaCO_2$ leading to increased arterial pulmonary hypertension [31, 33, 34], right ventricle failure and possibly increased mortality [31, 35–37]. Other unfavourable effects of hypercapnia have been described [15], and the current trend is to be more cautious with excessively high $PaCO_2$. "Too little of a good thing" [24] progressively shifted to "too much or too little of a good thing" [15], and it may be now discouraged to keep the $PaCO_2$ above 50 mmHg [35, 36]. There is a strong physiological rationale to avoid severe hypercapnia, leading to increased pulmonary hypertension, right ventricle dysfunction and peripheral vasodilatation [17, 21, 31]. However, the maximum $PaCO_2$ or minimum pH that may be tolerated is still debated. The values of 48 or 50 mmHg above which there is an increase in mortality came from observational studies that showed an association between severe hypercapnia with acidosis [35, 36, 38, 39] and mortality, but the direct causal effect remains unclear [40]. The severity of the acidosis and hypercapnia are certainly related in part to the severity of the patients.

In this regard, the negative impacts of hypocapnia are very well described [41], and the clinical impact may be at least as relevant [38, 42] and must be kept in mind when setting the ventilator. In conclusion, both severe hypocapnia and severe hypercapnia should be avoided. Therefore, optimized ventilator settings immediately after intubation and throughout the duration of invasive mechanical ventilation are required. For this, in addition to the reduced tidal volume, optimal settings of the respiratory rate, taking into account the dead space, must be put in place.

8.3 How to Set the Initial Respiratory Rate in Critically Ill Patients with Low or Very Low Tidal Volumes?

To ensure adequate CO_2 removal and to target moderately increased (below 50 mmHg) or normal $PaCO_2$, several actions are possible. The main ones are the increase in the respiratory rate and the minimization of the instrumental dead space [10].

It is easy to provide charts for the tidal volume based on gender and height and predicted body weight (PBW) to provide 6 or 8 ml/kg PBW to the patients. However, there are no clear recommendation and clues for the initial setting of the respiratory rate and therefore minute ventilation. This may be more a habit or intuitions and by experience: RR is set around 10 breaths/min in the operating room and around 20 breaths/min in newly intubated critically ill patients and sometimes increased to 25 or 30 in ARDS patients. A classical recommendation for minute ventilation is 100 ml/kg PBW/min (for instance, used to set the ASV mode [43] and recommended since 1955 [44]). However, in order to get a reasonable level of $PaCO_2$, 100 ml/kg PBW/min is not appropriate for most critically ill patients [10]. Ventilator settings in the operating room or in critically ill patients (in the emergency department and in the ICU) are very different, leading to minute ventilation around 100 ml/kg/min PBW in the operating room and at least 150 ml/kg/min PBW in critically ill patients. To reach 100 ml/kg PBW/min with 8 ml/kg PBW, a respiratory rate around

12 breaths/min should be used. In most severe patients, such as ARDS patients, a tidal volume of 6 ml/kg PBW associated with a respiratory rate of 25 breaths/min allows to get a minute ventilation of 150 ml/kg PBW/minute. These are two different worlds in terms of minute ventilation to match with patient's needs (Fig. 8.1). It should be noted that in case of high respiratory rate (greater than 20 breaths/min), the inspiratory flow must be kept high (greater than 40 l/min and up to 80 l/min) to promote low inspiratory time and sufficient expiratory time to avoid intrinsic PEEP [45].

Other measures to reduce $PaCO_2$ such as the use of an inspiratory pause have been proposed [46–48], but the effects are marginal compared to the increase in respiratory rate and the decrease in dead space and contradictory with the use of a high respiratory rate. The risk of an end-inspiratory pause prolonging the inspiratory time and reducing the expiratory time is to promote intrinsic PEEP in the case of high respiratory rate [45]. The utilization of ECMO or $ECCO_2R$ has been proposed to manage severe hypercapnia or to implement ultra-protective ventilation [49–52]. However, these complex and expensive techniques, associated with significant complications, should only be used if the simple measures described here (increase in respiratory rate and optimization of instrumental dead space) have been implemented [18, 53, 54].

In addition to the tidal volume and respiratory rate, the other major parameter to consider when initiating mechanical ventilation is the total dead space, including instrumental dead space. For this last parameter, the humidification strategy has a major impact.

8.4 What Is the Dead Space During Invasive Mechanical Ventilation?

The instrumental dead space is frequently overlooked during mechanical ventilation. Yet, many studies showed its large impact on the work of breathing during assisted ventilation [55–57] and on alveolar ventilation (CO_2 elimination) during controlled ventilation [16, 58–61]. Surprisingly, however, in many studies evaluating respiratory mechanics in ARDS or in COVID-19 patients, the instrumental dead space is not provided nor mentioned, even when V_D/V_T is evaluated.

The different parts of the dead space in mechanically ventilated patients are shown in Fig. 8.2. From the lungs to the Y-piece, this volume represents the "volume with CO_2 rebreathing" and the "wasted part of the respiration", which makes the gas exchanges less efficient [14, 62]. The alveolar dead space is the part of the lung that is ventilated but not perfused (capillary micro-thrombosis, capillary compression by overdistention), and it may be reduced by limiting overdistention; the dead space of

the airways is difficult to modify and is mildly increased by PEEP and bronchodilation; the instrumental dead space is the easiest to modify and may account for almost half of the total dead space [16, 17]. The instrumental dead space includes the heat and moisture exchanger at the Y-piece, the CO_2 sensor, the connections, the catheter mount, the flex tube, etc. Using a heated humidifier instead of a heat and moisture exchanger is a very efficient way to reduce this dead space [16, 58–61]. This is recommended in the most recent guidelines to manage ARDS patients [5].

8.5 Impact of the Instrumental Dead Space on V_D/V_T and Alveolar Ventilation During Lung-Protective Ventilation

Alveolar ventilation (Valv) is the efficient part of the minute ventilation for gas exchange and CO_2 elimination [62].

$$\text{Valv} = \text{RR} \times \left(V_T - V_D \right) = \text{RR} \times V_T - \text{RR} \times V_D$$

The utilization of small tidal volumes (V_T) and high respiratory rates (RR) has several consequences in terms of alveolar ventilation and impact of the dead space. Firstly, it is easy to understand that **V_D/V_T increases as tidal volume decreases** if V_D remains constant (Fig. 8.4a). The weight of dead space increases in proportion of tidal volume decrease for a constant minute ventilation. Secondly, the dead space which is the "wasted part of the breath" intervenes more frequently when respiratory rate increases.

Consequently, for a steady minute ventilation, when the respiratory rate or the dead space is increased, **alveolar ventilation is reduced** (Fig. 8.4b). If the respiratory rate is increased in proportion of the decrease in tidal volume, the alveolar ventilation will be reduced, and $PaCO_2$ will be increased. For example, if the settings are modified from 6 ml/kg PBW × 25 (150 ml/kg/min of minute ventilation) to 5 ml/kg PBW × 30 (150 ml/kg/min of minute ventilation), the alveolar ventilation will be lower. With an average instrumental dead space, to keep Valv constant with 5 ml/kg PBW of tidal volume, the respiratory rate should be 34/min (with 170 ml/kg PBW/min). This explains why reduction of the instrumental dead space is recommended in the situations of lung-protective ventilation [5] (i) by removing useless connectors (only closed-suction connector is really necessary) and (ii) by using HH instead of HME to humidify gases. This is also why ultra-protective lung ventilation may be implemented without ECMO or ECCOR, only when the instrumental dead space is minimized [53, 54].

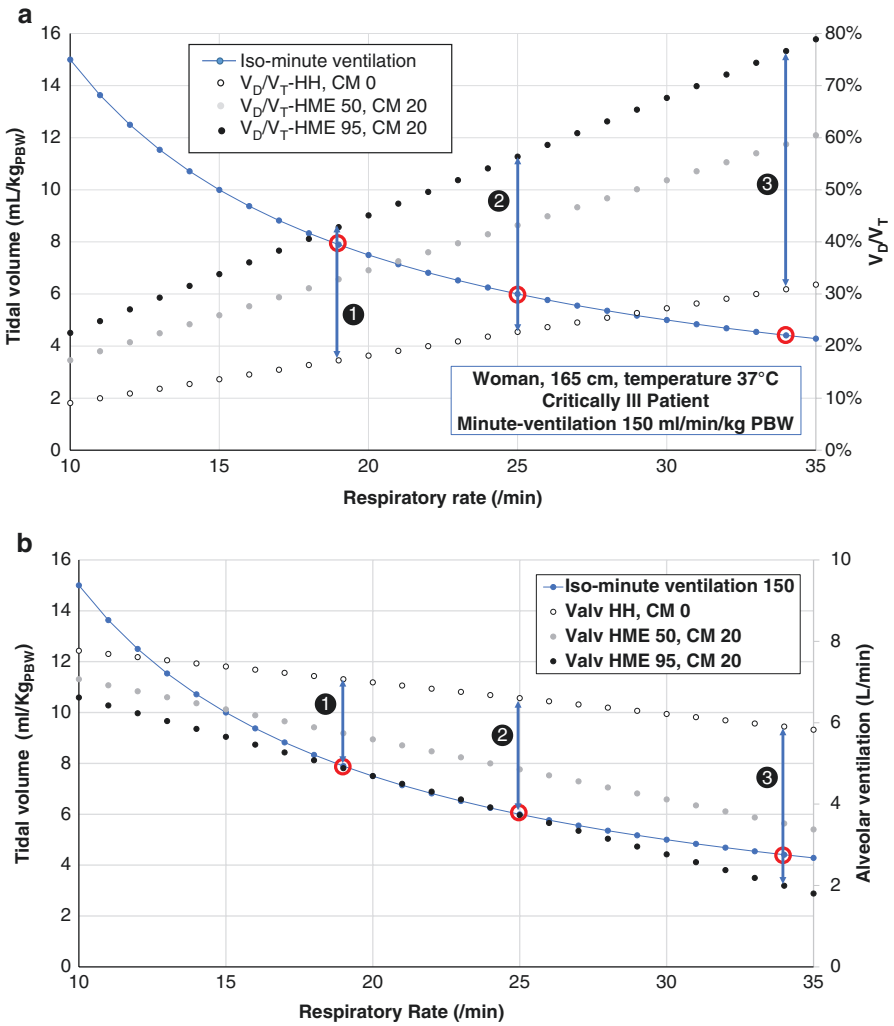

Fig. 8.4 Impact of instrumental dead space on V_D/V_T (**a**) and on alveolar ventilation (**b**) in critically ill patients with different instrumental dead spaces. The example used for the calculations is the case of a woman of 165 cm, PBW 57 kg. The blue line represents the iso-minute ventilation for 150 ml/kg PBW/min (8.5 l/min with PBW of 57 kg). In setting ❶, with a V_T of 8 ml/kg and a RR of 19 breaths/min, V_D/V_T is 17% with the lowest instrumental dead space and 43% with a higher dead space; alveolar ventilation went from 4.9 l/min to 7.1 l/min. When increasing the respiratory rate and decreasing the tidal volume (settings ❷ and ❸), the difference is even more striking. In the most severe situation, reflecting a low compliance requiring ultra-protective ventilation (case ❸) with a TV of 4.4 ml/kg and a RR of 34 breaths/min, V_D/V_T is 31% with the lowest instrumental dead space and 77% with a higher dead space. In this situation, alveolar ventilation goes from 6.0 to 2.0 l/min. *HH* heated humidifiers *HME* heat and moisture exchangers, *CM* catheter mount

8.6 Impact of Dead Space Reduction on Respiratory Parameters with Constant Alveolar Ventilation

The previous figures showed the impact of the dead space on alveolar ventilation (CO_2 clearance). Figure 8.5a and b shows that with a constant alveolar ventilation, it is possible to substantially decrease the respiratory rate (with constant tidal volume) (Fig. 8.5a) or the tidal volume (with constant respiratory rate) (Fig. 8.5b) when decreasing the dead space.

If the $PaCO_2$ is maintained within reasonable values (<50 mmHg based on several authors [35, 36]), the reduction of the instrumental dead space will allow a reduction of the respiratory rate (Fig. 8.5a) or a reduction of the tidal volumes (and plateau pressures [16, 59]) (Fig. 8.5b) while maintaining constant the alveolar ventilation (and $PaCO_2$). Both reduction of the respiratory rate and tidal volume associated with reduced instrumental dead space would also reduce mechanical power [19]. In addition, the reduction of the instrumental dead space reduces the ventilatory ratio [19, 63]. In the same patient, after reduction of the dead space, the ventilatory ratio would drop significantly, as the $PaCO_2$ will decrease. Similarly, the mechanical power which is associated with mortality in patients with ARDS will decrease just by decreasing the instrumental dead space if the $PaCO_2$ is maintained constant with reducing the respiratory rates. High mechanical power likely reflects a more severe disease with higher pressures, lower compliance requiring lower tidal volumes and higher respiratory rates. There is no evidence that the reduction of this parameter would decrease mortality, more than a decrease of the plateau pressure or driving pressure would decrease mortality. Ventilatory ratio [64] and mechanical power [65] are new markers of severity of ARDS but cannot be determined without taking into account the instrumental dead space (and mainly the humidification strategy used).

We have developed a free educational application, VentilO, to facilitate the initial management of protective mechanical ventilation (tidal volume, respiratory rate and dead space optimization). This tool evaluates the alveolar ventilation required based on the height, the gender (providing the predicted body weight), the actual weight, the temperature, the type of patient and the estimated dead space. Based on these data, it provides recommendations for tidal volume and respiratory rates.

In summary, in critically ill patients, the minute ventilation necessary to maintain $PaCO_2$ within a reasonable range is frequently at or above 150 ml/kg PBW/min. In non-ARDS patients if 8 ml/kg PBW is the targeted volume, a respiratory rate around 20 breaths/min may be adequate; with a tidal volume of 6 ml/kg PBW, respiratory rate around 25 breaths/min may be necessary (e.g., COVID patients). In severe ARDS with low compliance, requiring tidal volumes of 6 ml/kg PBW or lower to maintain plateau pressure below 30 cmH_2O, respiratory rate should be set at 25–30 breaths/min or even higher. The utilization of a heated humidifier in these situations to humidify and warm gases delivered to intubated patients allows minimizing the instrumental dead space and a better control of the $PaCO_2$. In most severe patients, with tidal volumes equal or below 6 ml/kg PBW, the minimization of the dead space is mandatory [54]. In CARDS patients (COVID-19 ARDS) , the same principles apply [20, 66].

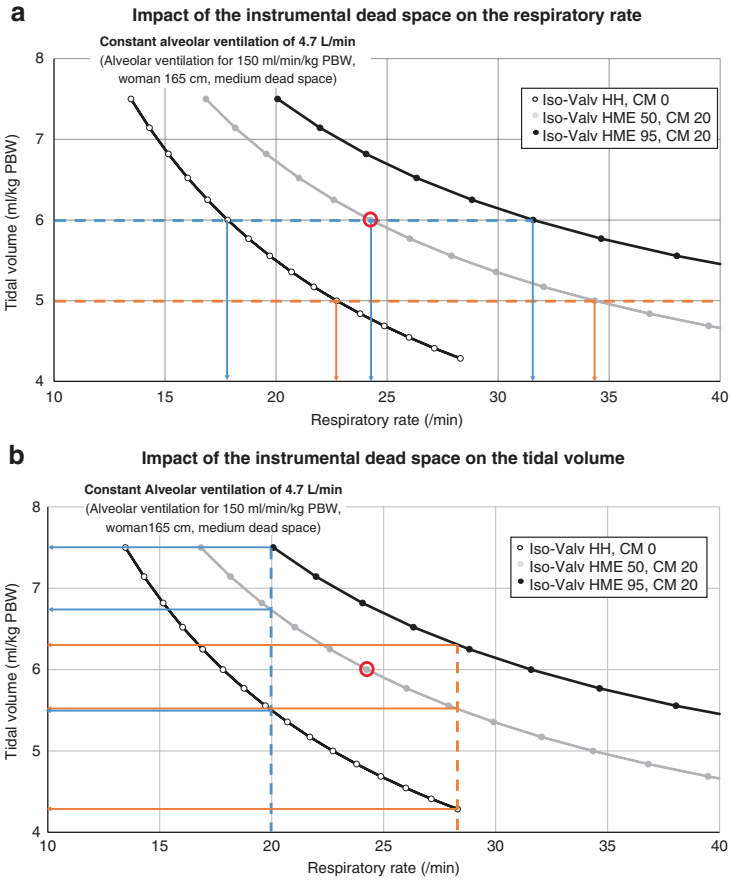

Fig. 8.5 Impact of different instrumental dead space on the respiratory rate (**a**) and the tidal volume (**b**) to maintain a constant alveolar ventilation in critically ill patients. The example used for the calculations is the case of a woman of 165 cm, PBW 57 kg. The target alveolar ventilation is 4.7 l/min which is the alveolar ventilation in this patient with a minute ventilation of 150 ml/kg/min PBW and with a medium instrumental dead space (HME 50 ml, catheter mount and connections 20 ml). The different lines represent the iso-alveolar ventilation lines (4.7 l/min) and the different combinations of respiratory rate and tidal volumes to attain this alveolar ventilation. Based on the application VentilO calculations. (**a**) This figure shows the potential reduction of respiratory rate when reducing the instrumental dead space to keep constant alveolar ventilation (4.7 l/min) for a constant tidal volume. For example, for a tidal volume of 6 ml/kg PBW (blue lines), the respiratory rate required is 32 breaths/min with the highest dead space and 18 breaths/min with the lowest dead space. For a tidal volume of 5 ml/kg PBW (orange lines), the respiratory rate required is very high (above 40 breaths/min) with the highest dead space, 34 breaths/min with intermediate dead space and 23 breaths/min with the lowest dead space. *HH* heated humidifiers, *HME* heat and moisture exchangers, *CM* catheter mount. (**b**) This figure shows the potential tidal volume reduction when reducing the instrumental dead space to keep constant alveolar ventilation (4.7 l/min) for a constant respiratory rate. For example, for a respiratory rate of 20 breaths/min (blue lines), the tidal volume required is 7.5 ml/kg PBW with the highest dead space and 5.5 ml/kg with the lowest dead space. This will translate in a gain in plateau pressure or driving pressure related to the pulmonary compliance. For a respiratory rate of 28 breaths/min (orange lines), the tidal volume required is 6.3 ml/kg with the highest dead space and 4.2 ml/kg with the lowest dead space. Ultra-protective ventilation with tidal volumes around 4 ml/kg cannot be achieved with excessive dead space as previously shown [54]. *HH heated humidifiers*, *HME* heat and moisture exchangers, *CM* catheter mount

Instrumental dead space may be very high (above 100 ml) when counting HME, catheter mount, connectors and endotracheal tube. Most efficient HMEs have usually a volume above 50 ml (up to 90 ml) [68], catheter mount may have a volume of 20–60 ml, and many connectors may be used in patients (CO_2 cuvette, closed suction and other adaptors for inhalation therapies) and may represent an important additional dead space.

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