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REVIEW

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Prophylactic protective ventilation: lower tidal volumes for all critically ill patients?

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Abstract High tidal volumes have historically been recommended for mechanically ventilated patients during general anesthesia. High tidal volumes have been shown to increase morbidity and mortality in patients suffering from acute respiratory distress syndrome (ARDS). Barriers exist in implementing a tidal volume reduction strategy related to the inherent difficulty in changing one's practice patterns, to the current need to individualize low tidal volume settings only for a specific subgroup of mechanically ventilated patients (i.e., ARDS patients), the difficulty in determining the predicated body weight (requiring the patient's height and a complex formula). Consequently, a protective ventilation strategy is often under-utilized as a therapeutic option, even in ARDS. Recent data supports the generalization of this strategy prophylactically to almost all mechanically ventilated patients beginning immediately following intubation. Using tools to rapidly and reliably determine the predicted body weight (PBW), as well as the use of automated modes of ventilation are some of the potential solutions to facilitate the practice of protective ventilation and to finally ventilate our patients' lungs in a more gentle fashion to help prevent ARDS.

Keywords Protective ventilation · Acute lung injury · Acute respiratory distress syndrome · Mechanical ventilation · Low tidal volume · Predicted body weight

Introduction

The use of high tidal volume (VT), which we define as a VT >10 ml/kg of PBW, has been heavily influenced by the landmark paper by Bendixen et al. [1] in 1963, demonstrating the promotion of atelectasis in anesthetized patients when low tidal volumes were used as compared with higher tidal volumes. Subsequently, the use of high VT has been promoted to prevent atelectasis in anesthetized patients and by extension has influenced all mechanically ventilated patients, even in the case of ARDS [2–4]. Ventilator-induced lung injury related to high tidal volumes was first described in animals in the 1970s [5–7] and later confirmed in clinical studies [8, 9]. Lung protective ventilation with low tidal volumes is frequently considered the standard of care for patients suffering from acute respiratory distress syndrome (ARDS) [10–12]. In ARDS, there is a breakdown of normal lung architecture, loss of functioning lung units and the development of high permeability pulmonary edema, all of which result in clinically stiff, non-compliant and heterogeneous lungs [13]. High VTs resulting in high alveolar pressures in this setting can promote a wide array of local and systemic adverse effects, known as ventilator-induced lung injury (VILI) [7]. Mechanistically, these pathophysiologic changes occur from the

direct effect of high pressure on the lung, barotrauma, from the damage caused by lung overdistension, volutrauma, from the shear stress of repetitive opening and closing of alveoli, atelectotrauma, and from the generation of cytokines and an inflammatory cascade, resulting in biotrauma [13]. Protective ventilation refers to the use in ARDS patients of low VT, often in the range of 4–8 ml/kg of PBW. Currently, this strategy is only recommended in a small subset of mechanically ventilated patients; those who have ARDS [10–12]. However, there is mounting evidence that high tidal volumes can be injurious to the lungs and other organ in patients without ARDS. Data from Gajic et al. have suggested that ARDS can be a hospital-acquired event akin to hospital-acquired infections, and high tidal volume use in mechanically ventilated patients was among the strongest risk factors for the development of hospital-acquired ARDS [14–16]. We will review the current literature concerning the use of prophylactic protective ventilation in patients without ARDS criterion and highlight important challenges that limit the successful implementation of protective ventilation in clinical practice. This article focuses on prevention of ARDS rather than on its treatment as the vast majority of ventilated patients are not initially affected by ARDS [14, 17, 18].

A brief history of protective ventilation

In 1963, a seminal paper by Bendixen [1] in the New England Journal of Medicine demonstrated that the use of higher VTs during anesthesia (18 patients undergoing laparotomy) resulted in less acidosis and improved oxygenation compared to lower VTs. These findings were important at this time as both hypoxemia and acidosis were of concern for anesthesiologists given the limited capacity to monitor patients' blood gases in this era. This important paper also popularized the concept of atelectasis in mechanically ventilated patients. Nearly 50 years later, authoritative anesthesiology textbooks continued to recommend the use of VTs between 10–15 ml/kg for patients undergoing mechanical ventilation in order to avoid atelectasis and hypoxia [3, 4], and many studies have been performed in patients with ARDS with a variety of high VTs ranging from 10 to 24 ml/kg [2, 19]. Initial animal data demonstrated that high tidal volume could be injurious to the lung, and pioneers in the field proposed strategies of "permissive hypercapnia" based on tidal volume reductions [20]. However, it was many years later that two randomized clinical trials (RCTs) in humans demonstrated improved outcomes with the use of lower VTs [8, 9]. Intense debate followed with a meta-analysis by Eichaker that also included three "negative" RCTs and suggested that the primary conclusion should be that high tidal volumes (12 ml/kg of PBW) and corresponding plateau pressures have deleterious side effects [21–24]. To be more precise, the transmitted pressure to the alveoli or transpulmonary pressure, calculated as the difference between the alveolar and pleural pressures, is what causes alveolar trauma [25]. Due to the difficulty in calculating transpulmonary pressures, one should monitor and maintain the plateau pressure below 30 cmH_2O. Currently most authors recommend the use of protective ventilation with 6–8 ml/kg of PBW in ARDS patients [10–12]. However, in less ill patients with high lung compliance, tidal volume reduction may not be beneficial [26]. The recommendation for prophylactic protective ventilation using lower tidal volumes in patients without ARDS is currently less established.

Protective ventilation in patients without lung injury

Once the lung has been "primed" by an initial insult such as pneumonia, sepsis, non-cardiogenic shock, major trauma, multiple transfusions or cardiopulmonary bypass [27], injurious mechanical ventilation with high tidal volumes leading to high alveolar and transpulmonary pressures can then amplify a pulmonary and systemic inflammatory response leading to VILI and "iatrogenic ARDS" (Fig. 1); [14–16]. This process is usually labeled as the "multiple-hit theory" of ARDS [28, 29]. Many patients admitted in ICUs have at least one of these risk factors, and it was shown that very high tidal volumes, up to 18 ml/kg of PBW, are still delivered to ICU patients [15, 30]. Most of the studies comparing "protective ventilation" with low VT and high PEEP to "conventional ventilation" with high VT and low PEEP in non-ARDS patients demonstrate a beneficial impact of the protective ventilation strategy on inflammation, oxygenation or clinical outcome data (Tables 1, 2); [15, 16, 30–50]. However, it must be highlighted that most of the currently available studies have small sample sizes and report mainly on inflammatory biomarkers, and few studies have data on meaningful patient outcomes. Patients who appear to benefit most from prophylactic protective ventilation in these studies are those who undergo high-risk surgery (e.g., cardiac bypass, pneumonectomy) or who are critically ill and require ICU admission [15, 16, 30, 38, 39, 41, 44, 45, 48]. These patients may therefore benefit from a strategy of tidal volume reduction from the time of initiation of mechanical ventilation to reduce the risk of developing ARDS. Large randomized controlled studies are ongoing to assess the impact of protective ventilation in other populations [51].

Applying prophylactic protective ventilation at the initiation of mechanical ventilation: practical issues

When?

It has been previously shown that initial ventilator settings are often unchanged following initial intubation [15, 30];

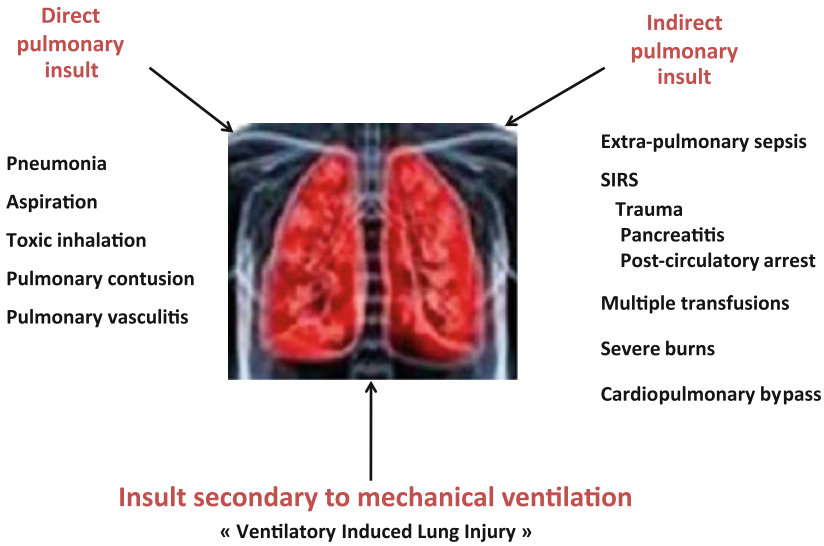

Fig. 1 Multiple hit theory for acquired ARDS. In addition to physiological and/or biochemical stress that the lungs in critically ill patients are exposed to, mechanical ventilation per se can represent an additional insult if protective ventilation is not utilized. Prevention of iatrogenic ARDS requires early application of protective ventilation

meanwhile pulmonary damage can happen after only a few hours of mechanical ventilation [38]. Moreover, ARDS is frequently underrecognized by clinicians [52, 53] or recognized with delay. In a recent study, it was shown that patients with mild ARDS were exposed to injurious ventilation from 40.6 ± 74.6 h before to 26.9 ± 77.3 h after implementation of an electronic alert system [54]. Prophylactic protective ventilation should therefore be implemented as soon as patients are intubated. Using this strategy by default for all mechanically ventilated patients earlier rather than to a limited population of ARDS patients later in their course of disease (after recognition of the ARDS criterion) is likely to increase the benefits of tidal volume reduction. The application of lower tidal volume is easily feasible during initial controlled ventilation, which may last a few hours or up to several days in more severely ill patients. Of note, there are no data to support delaying the switch from controlled to assisted ventilation in patients without ARDS in order to control the VT. Indeed, spontaneous ventilation should be promoted early in most patients even if VT control is not easily feasible with assisted ventilation, which is often the case when critically ill patients have a high respiratory drive [55]. This remains a difficult and unresolved issue.

How?

Tidal volume

In patients without ARDS, current evidence suggests that a VT between 6–8 ml/kg PBW in patients at risk of ARDS could be used safely and with potential benefits, and in patients without risk factors, a VT ≤10 ml/kg PBW may be appropriate [56]. It must be emphasized that the PBW and not the actual body weight (ABW) should be used to calculate tidal volume (Fig. 2). The use of ABW may overestimate the required VT especially in patients with a BMI >25, and this has been associated with increased organ failure [30]. This is of growing importance considering the current epidemic of obesity. When the first RCTs were initiated in the 1980s, 10 % of the US population had a BMI over 30. This has now increased to almost 40 % of the population in the US and also affects a large proportion of developing countries as well [57, 58].

PEEP and FiO_2

What Bendixen described in 1963 is still true: the utilization of lower tidal volumes can result in atelectasis, hypoxemia and acidosis. However, since Bendixen's paper, several physiological reports have shown that the use of PEEP could prevent atelectasis [59]. The effect of PEEP was particularly well demonstrated in obese patients [60], and moderate levels of PEEP should be applied with the use of lower VTs to avoid atelectasis. Although the optimal level of PEEP is still controversial, the use of zero PEEP (ZEEP) has been associated with worse outcomes, including increased hypoxemia, ventilator-associated pneumonia as well as hospital mortality [17, 61]. The optimal level of PEEP in prophylactic protective ventilation remains unclear. In patients without ARDS, PEEP levels between 5 and 12 cmH_2O have been used in conjunction with low tidal volume and usually ≥8 cmH_2O (Tables 1, 2). Therefore, to avoid atelectasis, we suggest starting with a PEEP level of 8 cmH_2O (or more in obese patients because of increased pleural pressures) and titrating depending on the FiO_2 and the hemodynamic status of the patient. New tools estimating end expiratory lung volumes could be helpful to titrate PEEP in this situation [62].

Table 1 Impact of perioperative ventilation strategy

Study	Study design	Patient population	Number of patients	Control ventilatory settings		Experimental ventilatory settings		Main findings with protective ventilation
				Tidal volume (ml/kg)	PEEP (cmH_2O)	Tidal volume (ml/kg)	PEEP (cmH_2O)	
Wrigge et al. [31]	RCT	Elective non-thoracic surgery	39	15	0	6 6	0 10	No difference in inflammatory markers
Chaney et al. [32]	RCT	CABG	25	12	≥5	6	≥5	Improved respiratory mechanics
Koner et al. [33]	RCT	CABG	44	10	0	6	5	No difference in inflammation. Increased oxygenation with PEEP
Wrigge et al. [34]	RCT	Abdominal and thoracic surgery	64	12–15	0	6	10	No difference in inflammatory markers
Schilling et al. [35]	RCT	Thoracic surgery	32	10	3	5	[3]	Decreased TNF-α and sICAM-1
Wrigge et al. [36]	RCT	CABG	44	12	–[a]	6	–[a]	Decreased TNF in BAL
Reis Miranda et al. [37]	RCT	CABG	62	6–8	5	4–6	10	More rapid decrease in pro-inflammatory cytokines
Zupancich et al. [38]	RCT	CABG	40	10–12	2–3	8	10	Decrease in pro-inflammatory cytokines after cardiopulmonary bypass
Fernández-Pérez et al. [39]	OBS	Pneumonectomy	170	8.3 (mean)	–	6.7 (mean)	–	VT was a risk factor for acute respiratory failure
Choi et al. [40]	RCT	Elective abdominal surgery	40	12	0	6	10	Decrease in coagulation activation after 5 h of MV
Michelet et al. [41]	RCT	Esophagectomy	52	9	0	5	5	Decrease in inflammatory markers Improved oxygenation Decrease in MV duration
Licker et al. [42]	COH	Pneumonectomy	1,091	7.1[b]	3.3[b]	5.3[b]	6.2[b]	Reduced risk of ALI (OR 0.34, $P = 0.002$)
Weingarten et al. [43]	RCT	Abdominal surgery	40	10	0	6	12	Improved respiratory mechanics and oxygenation. No difference in biomarkers
Yang et al. [44]	RCT	Pulmonary lobectomy	100	10	0	6	5	Less pulmonary dysfunction within 72 h post-op
Sundar et al. [45]	RCT	CABG and valves	149	10	≥5[a]	6	≥5[a]	Less intubated patients after 6 h Less reintubation
Lellouche et al. [30]	OBS	CABG and valves	3,434	–	–	<10 10–12 >12	–	Less organ dysfunction and ICU length of stay with lower VT

RCT randomized controlled study, *OBS* observational study, *COH* cohort study, *MV* mechanical ventilation, *BAL* bronchoalveolar lavage, *TNF* tumor necrosis factor, *VT* tidal volume, *CABG* coronary artery bypass graft

[a] PEEP titrated based on a PEEP/F_IO_2 ladder

[b] Mean results

In addition, a reduction in the levels of FiO_2 should be undertaken as levels above 60 % can cause denitrogenation-atelectasis [63, 64]. It is well accepted that SpO_2 targets must be reduced in the case of ARDS patients to 88–92 % [11, 65], and this also should also be considered in other patient populations. SpO_2 should be kept above 92 % to maintain a SaO_2 above 90 % [65]. However, while hyperoxia toxicity is now well established, there is no upper limit that is recommended [66–68], and with the exception of abdominal surgeries where hyperoxia may be beneficial in the reduction of surgical site infections, there is no evidence suggesting clinical benefits for maintaining a SpO_2 above 96 % [69].

When lower VTs are used, the respiratory rate needs to be increased to avoid respiratory acidosis and metabolic complications such as acute hyperkalemia, especially when patients have high minute ventilation before intubation. A starting respiratory rate of 20 or more seems reasonable to avoid severe acidosis following initial intubation with tidal volumes below 10 ml/kg of PBW. In order to maintain adequate minute ventilation, it may be required to aggressively increase the respiratory rate,

Table 2 Impact of ventilation strategy in the ICU

Study	Study design	ICU	Number of patients	Control ventilatory settings		Experimental ventilatory settings		Main findings with protective ventilation
				Tidal volume (ml/kg)	PEEP (cmH_2O)	Tidal volume (ml/kg)	PEEP (cmH_2O)	
Lee et al. [46]	RCT	Surgical	103	12	5	6	5	Trend for decreased pulmonary infections and decrease in MV duration
Gajic et al. [15]	COH	Medical/surgical	332	–	–	–	–	OR for ALI = 1.3 with VT >6 ml/kg
Gajic et al. [16]	COH	Medical/surgical	3,261	–	–	–	–	OR for ARDS = 2.6 with VT >700 ml
Mascia et al. [50]	OBS	Neurocritical	86	9.5[b]	3.7[b]	10.4[b]	4.2[b]	OR for ALI = 5.4 with high VT >9 ml/kg
Determann et al. [48]	RCT	Medical/surgical	150	10	–[a]	6	–[a]	RR for ALI = 5.1 with high VT. Decreased inflammatory cytokines with low VT
Pinheiro de Oliveira et al. [49]	RCT	Medical/surgical	20	10–12	5	5–7	5	Decreased BAL cytokines with low VT
Mascia et al. [47]	RCT	Medical/surgical	118	10–12	3–5	6–8	8–10	Increase in eligible and harvested lungs with low VT

RCT randomized controlled study, *OBS* observational study, *COH* cohort study, *MV* mechanical ventilation, *VT* tidal volume, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *OR* odds ratio

[a] PEEP titrated based on a $PEEP/F_IO_2$ ladder

[b] Mean results

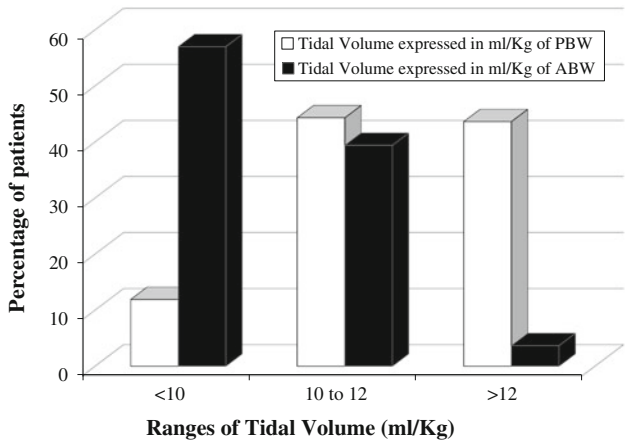

Fig. 2 Proportion of patients receiving tidal volumes <10, from 10 to 12 or >12 ml/kg expressed as predicted or actual body weight (ABW or PBW) in a cohort of 3,434 patients after cardiac surgery (adapted from Ref. [30])

sometimes above 30 breaths/min. This may lead to the development of dynamic hyperinflation and auto-PEEP, which can have significant negative respiratory and hemodynamic consequences [70]. Due to short time constants and low lung compliance in patients with ARDS, this risk is usually limited below 30 breaths/minute [71], but in patients with normal lung compliance and longer time constants, the possibility of auto-PEEP may incur at lower respiratory rates. Thus, the ability to recognize patients at risk for auto-PEEP as well as to accurately recognize the presence of dynamic hyperinflation from abnormal ventilator waveforms is fundamental to safe clinical practice [70]. In addition, the humidification system used with the ventilator is particularly important and can be a significant contributor to increased respiratory acidosis if low tidal volumes and high respiratory rates are used. To reduce the severity of hypercapnia, reduction of dead space can be easily accomplished by using a heated humidifier instead of a heat and moisture exchanger [72]; (Table 3).

Overcoming barriers to implement strategies of tidal volume reduction

It takes many years to implement research findings into clinical practice, a process referred to as knowledge translation [73]. Indeed, despite evidence showing that a reduced VT strategy is associated with improved outcomes in ARDS patients, clinicians still routinely use VTs greater than 10 ml/kg [74, 75]. Eight years following the original landmark ARDS Network paper, Umoh et al. [76] still found that only 46 % of eligible patients received low VT ventilation in a multicenter study. Studies showing the most impressive implementation of protective ventilation

Table 3 Recommended initial lung-protective mechanical ventilator settings following intubation in patients without ARDS

Initial ventilator settings	Patients without risk factors for ARDS	Patients with risk factors for ARDS*
VT (ml/kg PBW)	<10	6–8
Respiratory rate (breath/min)[a]	≥15	≥20
PEEP (cmH_20)	≥5	≥8
FiO_2 (%)[b]	<60	<60
Target SpO_2 (%)[c]	92–96	92–96
Humidification device[d]	HME	HME

VT tidal volume, *PBW* predicted body weight, *HME* heat and moisture exchangers

*sepsis, trauma, blood transfusions, and cardiopulmonary bypass

[a] Higher respiratory rate may be required in the case of high minute ventilation, acidosis or hyperkalemia before intubation

[b] The lowest FiO_2 to achieve an acceptable SpO_2 should be used

[c] If FiO_2 requirements are above 60 %, a target SpO_2 of 88–92 % should be tolerated

[d] The heterogeneity of the HME should be known, and if severe respiratory acidosis occurs, heated humidifiers should be used instead [89]. These settings can be used as long as patients require controlled ventilation

were carried out in centers participating in mechanical ventilation networks or used active educational tools to improve care [77, 78], but this does not reflect real-life practice, where protective ventilation in ARDS patients is often less successfully applied [79]. Even in ARDS network centers participating in the ALVEOLI trial, tidal volume was not reduced to 6, but to 8 ml/kg PBW at baseline [80]. The habit of using large VTs >10 ml/kg for several decades and the known difficulty in recognizing patients who meet criteria for ARDS are some of the reasons for the low compliance with current low tidal volume guidelines [52, 53]. The generalization of protective ventilation to all "at risk" patients as soon as they are intubated would likely facilitate the implementation of protective ventilation and improve overall compliance.

Despite the attempt to use protective ventilation in everyday practice, the use of actual instead of predicted body weight (PBW) in the calculation of VT is a frequent error, leading to over-treatment with higher VTs (Fig. 2); [30, 81]. Interestingly, in a meta-analysis by Eichaker et al., the absence of a uniform method to express the VT was discussed; four different methods were used out of the five RCTs: PBW [8, 24], ideal body weight [23], dry weight [22] and ABW [9]. PBW in men is calculated as 50 (45.5 in women) +0.91 (height −152.4 cm) [8]. In many instances, the height of the patient is not immediately known. This is especially true outside of the surgical ICU (i.e., pre-hospital transport, emergency department, post-anesthesia recovery room or medical ICU) because surgical ICUs are more likely to have height and weight measurements because of the operative record. In addition, visual estimation of patient height and PBW is known to be inaccurate, and shorter female patients tend to be disproportionally affected [82, 83]. The ability to rapidly calculate PBW at the bedside is important. Novel devices such as applications on smartphones (e.g., *iAnthropometer ICU*), where one can quickly calculate the patients' height from the patient's lower leg length based on validated formulas and automatically derive the PBW and subsequent VTs are promising tools [84, 85]. This application was more accurate at calculating patient height than both the method of visual estimation and supine in-bed tape measurement [85].

Automated mechanical ventilation systems are another way to help implement protective ventilation. The new fully automated ventilator (IntelliVent^{TM}, Hamilton Medical, Bonaduz, Switzerland) was recently evaluated [86]. VTs were automatically reduced below 10 ml/kg of PBW after only a few minutes of mechanical ventilation, and the respiratory rate was automatically increased to maintain stable minute ventilation. These closed loop systems will likely become more widely available given the results of promising initial clinical evaluations and the expected rise in the number of mechanically ventilated patients in the future [87].

Conclusion

To recommend prophylactic protective ventilation to all intubated patients may not be justified; however, more liberal use of this treatment could safely be promoted following initial intubation and mechanical ventilation. In line with other authors, we recommend a VT of 6–8 ml/kg PBW in patients with risk factors for the development of lung injury [56], such as multiple transfusions, trauma, sepsis, or high-risk surgery. In other mechanically ventilated patients, we recommend the use of VTs below 10 ml/kg PBW from the initiation of mechanical ventilation. As was shown almost 50 years ago, small tidal volumes may induce derecruitment and atelectasis. The alternative to the use of high tidal volumes to avoid this complication is the use of moderate levels of PEEP. Compared to patients with ARDS who often have a significant amount of recruitable lung units and higher oxygenation requirements, the amount of PEEP required for patients without ARDS is likely to be less, and based on limited current evidence, we suggest an initial setting of 8 cmH_2O, which should be titrated based on the individual patient's oxygenation requirements. Future prospective clinical trials will be required to better define the optimal VT and PEEP in patients in the ICU or operating room who are at risk for ARDS in order to reduce the risk of hospital acquired ARDS. Considering the proven safety of this approach, the physiologic rationale and the current evidence, this prophylactic protective ventilation strategy can be recommended for almost all mechanically ventilated patients who do not yet

have ARDS and particularly those with risk factors to prevent progressive development of lung injury. Given the high prevalence of risk factors for ARDS and the unpredictability of developing ARDS throughout the course of one's illness, the implementation of a ventilation strategy that incorporates tidal volume reduction based on PBW and moderately high PEEP in the majority of intubated ICU patients and at initiation of invasive mechanical ventilation is reasonable [88]. This strategy has potential benefits, and there is little evidence of associated harm. Patients who may not benefit from this strategy are those who are otherwise healthy and are undergoing routine elective surgery.

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