

Spontaneous breathing during mechanical ventilation in ARDS

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Abstract

The objective of mechanical ventilation used in the management of Acute Respiratory Distress Syndrome (ARDS) is to ensure adequate tissue oxygenation and alveolar ventilation while limiting the patients' work of breathing and preventing further damage to the lungs. Although the "partial support" ventilation modes were initially developed to assist weaning or liberation from supported ventilation, they have gained increasing popularity as primary ventilation modes, even in patients in with severe acute pulmonary dysfunction. Allowing spontaneous breathing is known to alter both lung mechanics and physiological effects of ventilation, therefore has potential influence on important patho-physiological changes and

complications that occur. Spontaneous ventilation has the potential to improve outcomes in ARDS, and therefore is worthy of an intensivist's attention. A clinical trial of the use of pharmaceutical paralysis suggest a protective effect against worsening respiratory failure by ablating spontaneous breathing in ARDS. Overdistension of alveoli, even at low ventilator driving pressures may be as dangerous as high tidal volume (TV) controlled ventilation and thus naïve use of unrestricted spontaneous breathing techniques may be detrimental. As evidence of both improvement and deterioration exist the hypothesis remains controversial, and warrants a properly conducted randomised trial.

Keywords: Acute Respiratory Distress Syndrome (ARDS), mechanical ventilation, spontaneous ventilation, neuromuscular blocking agents, pressure support, airway pressure release ventilation, tidal volume, ventilator induced lung injury (VILI), oxygen, alveoli.

Introduction

A variety of ventilation modes have been employed to artificially deliver the work of breathing and assure gas exchange during acute severe respiratory failure from ARDS [1-3]. Classically, patient interaction with ventilators was discouraged, and the heavy sedation and paralysis commonly used in the most severe patients meant the modes were indistinguishable from pressure or volume controlled mechanical ventilation (CMV). These full ventilation modes were employed until the underlying acute respiratory dysfunction resolved sufficiently to allow weaning [4]. Many patients are able to be successfully extubated after a short trial using nearly any weaning

method [4]. Of those with difficulty tolerating unassisted spontaneous breathing, the limited trials available suggest that "weaning" is best achieved by either

- 1) allowing spontaneous breathing with a T-piece or continuous positive airway pressure (CPAP) or
- 2) Establishing spontaneous breathing and gradually reducing pressure support [1, 5].

Reduction in ventilation duration to a minimum is desirable goal and the earliest introduction of spontaneous breathing to achieve weaning is therefore essential [6]. The search for superior weaning techniques lead to the development of several partial support modes that permit some spontaneous breathing. Several have become popular as primary mechanical ventilatory modes in acute ARDS [7].

However, it remains unclear whether encouraging spontaneous ventilation in patients with acute severe ARDS, who are not capable of being ventilator free, is beneficial. The introduction of spontaneous breathing into ventilation potentially introduces many attendant prob-

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lems, including dys-synchrony, sedation, triggering, awareness and increased risk of accidental extubation. Synchronisation and machine responsiveness are essential if any benefit from spontaneous ventilation is to be realised. The last quarter century have seen significant advances in ventilator triggering [7]. In addition increased microprocessor speed has improved ventilator responsiveness. With innovations such as tube compensation and larger valves to prevent flow starvation, spontaneous breathing in patients with severe respiratory distress is now feasible [8, 9].

Are there potential benefits of maintaining spontaneous breathing in ARDS?

Acute Respiratory Distress Syndrome (ARDS) is characterized by lung inflammation and oedema. Recent Computed tomography studies in ARDS have created a clearer picture of factors affecting the regional distribution of ventilation [10, 11]. Localised compression effects caused by heart and subdiaphragmatic organs, coupled with a more cephalic displacement of dependent regions with volume loss, compared with the nondependent regions, probably from muscle inactivity in “full” ventilation [12]. When spontaneous breathing is maintained, ongoing diaphragm activity may produce higher trans-pulmonary pressure in the lower regions, near the diaphragm, preventing this collapse and thus reducing the incidence of atelectasis [13].

Most data on spontaneous breathing modes in ARDS relates to Airway pressure release ventilation (APRV). APRV ventilates by time-cycling between two pressure levels with a high-flow (demand) valve CPAP circuit allowing essentially unrestricted spontaneous breathing in any phase of the ventilator cycle. The “ventilator rate” is dependent upon the duration of both CPAP levels, while “tidal volume” is dependent upon the differential between upper and lower pressures along with the respiratory compliance. Minute ventilation is dependent upon this “rate” and the ventilated TV, along with the volume and rate of spontaneous breathing over the background of these pressure controlled volume changes. If no spontaneous breathing occurs, APRV is identical to conventional time cycled pressure-controlled ventilation.

Both experimental and clinical trials with ARDS suggest that allowing spontaneous breathing with APRV produces immediate improvement in gas exchange and systemic blood flow. This is probably achieved through improved gas distribution within functioning alveoli and reduced atelectasis [11, 14-17].

In a single trial of non-septic trauma patients receiving APRV or PCV, patient receiving APRV required less

sedation to maintain synchrony, less vasoactive support, shorter ventilation and shorter ICU stay compared to the PCV group [15].

Putensen, using the above study and other evidence of improved oxygenation, recommends techniques of mechanical ventilatory support that maintain, rather than suppress, spontaneous ventilatory effort, especially in patients with severe pulmonary dysfunction [18]. However other guidelines suggest that in sepsis induced ARDS Airway pressure release ventilation should be limited to use in controlled clinical trials or as rescue therapy in patients who have failed traditional lung protective strategies [19].

Maintaining adequate oxygenation while avoiding mechanical ventilation’s deleterious effects are major priorities for intensivists managing ARDS. Although the value of initial PaO₂/FIO₂ ratios in outcome prediction is debated, a patients with prolonged intractable hypoxemia have a worse prognosis than those in whom oxygenation improves [20, 21].

It would be easy to assume that any means to improve oxygenation during ARDS is justified. Unfortunately there is no robust data to suggest that improvement in arterial oxygenation is a surrogate outcome measure for mortality [22]. Management with nitric oxide, prone positioning or extracorporeal circulation have all successfully increased arterial oxygen status in ARDS, but none of these strategies improved survival [23-25]. Conversely the ARDSnet low tidal volume study, the low TV group had superior 28 day survival despite demonstrating worse oxygenation in the first three days of the study period [26]. Likewise, demonstration that spontaneous ventilation improves oxygenation cannot be taken as proof that improved outcome will follow.

Are there potential hazards of spontaneous breathing?

Pressure Support ventilation (PSV) is commonly used in many countries, both as primary ventilation and weaning modes [1-5]. Although PSV appears safe in acute phases of ARDS, it did not improve intrapulmonary shunt, VA/Q matching, or gas exchange [27]. PSV failure is more common in sicker patients with lower respiratory compliance, worse or longer ventilation dependency. Despite its widespread clinical advocacy and use, there is no clear evidence of benefit during the non-weaning phase.

Patient transferred to PSV frequently require lower levels of plateau pressure to support the same TV set in the mandatory mode.

Respiratory compliance is affected by both lung and chest wall compliance. In changing from controlled to spontaneous ventilation lung compliance remains unchanged, but increased synchrony through triggering may increase the chest wall compliance. Now, as the patient triggers the respiratory effort, the chest wall provides less active resistance to the distending lung. Another integral factor is the significant work performed by the patient in actively breathing. With spontaneous breathing, the diaphragm moves down, with an active expansion of the chest cavity. This develops a negative intrapleural pressure, which augments the pressure differential across the alveolar membrane when the pressure support is applied during inspiration.

The magnitude of the pressure generated by the patient and the ventilator combine, to create a trans-alveolar pressure, is undetected by standard monitoring, but has the potential for over-distension of alveolar and increased Ventilator induced lung injury (VILI). An example of how this can occur is given below.

breathing respiratory effort developed a negative 25 cm H₂O. This active work during spontaneous inspiration allows larger volumes to be delivered with the same or lower upper airway pressures. However, the pressure across the alveoli membrane was 18 cm H₂O during PCV using lung protective ventilation, but rose to 51 cm H₂O during the spontaneous breathing phase. When the same TV was delivered using PCV with sedation and paralysis, the trans-alveoli membrane pressure was also elevated to 51 cm H₂O.

Most clinicians would be concerned if a 70 kg patient was ventilated with PCV plateau pressure over 60 cm H₂O and 720 ml TVs (see CV 2), but many would be less concerned about 720 ml TVs in spontaneous triggered PSV with low plateau pressures. The above example demonstrates that the upper airway pressure may not reflect the distension of the alveolar in spontaneous breathing.

Animal studies of VILI were related to trans-pulmonary (or trans-alveolar) pressure, not to the upper

TABLE 1. SEE TEXT ABOVE

		CV 1 Sedation, Paralysis and Pressure Controlled Ventilation	SV1 Spontaneous ventilation with Pressure Support	CV 2 Sedation, Paralysis and Pressure Controlled Ventilation
A;	PEEP	+8	+8	+8
B:	Pressure support/Pressure control	+20	+18	+53
C=(A+B)	Plateau pressure	+28	+26	+61
	Tidal volume	390 mL	720 mL	720 mL
D	Oesophageal Pressure	+10	-25	+10
C- D	Trans alveoli pressure	+ 18	+ 51	+ 51

A 65 kg patient with severe ARDS is ventilated using PCV with standard lung protection parameters, aiming for TV of 6mL/kg and plateau pressures < 30 cm H₂O. (See table 1, PC1) Spontaneous breathing is then established with settings for pressure support less than the pressure control for PCV, delivering a peak pressure of 26 cm H₂O pressure. However, with spontaneous breathing, TV is now 720 ml, or 11mL/ kg (see SV1). As peak pressures are below the 30 cm H₂O threshold, the TV is not considered dangerous. With sedation and paralysis recommenced, the plateau pressure required to achieve 720 ml TV with PCV is 61 cm H₂O.

Measurement of oesophageal pressures showed +10 cm H₂O during PCV breaths, while during spontaneous

airway pressures routinely measured in clinical trials [28, 29]. The damaging pressure and distension relates to the alveoli membrane rather than to the entire lung system but in spontaneous breathing the pressure measured at the upper airway does not reflect the trans alveoli membrane pressure [29]. Oesophageal pressures measurements approximate pleural pressure and from these trans-alveolar pressures generated can be calculated. Oesophageal pressure measurement is not routine but ventilators are now available capable of measuring these additional pressures [30].

Prior to the ARDS net study there was little consistency in the TVs delivered to patients with severe ARDS [31]. Patients allowed to breath spontaneous in ARDS

have a huge variation in their TV, respiratory rates and arterial carbon dioxide [32]. It is now clear that mechanical ventilation using VT of 6 mL/kg ideal body weight improves outcome in patients with ARDS compared to use of larger TVs [26, 33]. In both the ARDS ventilation studies with positive outcomes, not only was TV limited (6 ml/kg during the acute phase), but also plateau pressures (< 30 cm H₂O in the ARDSnet trial, < 20 cm H₂O driving pressure above PEEP in the Amato study). Spontaneous breathing was discouraged both by the mode ventilation and level of sedation used. However, as trans-alveolar pressures were not recorded, and TVs not controlled during weaning, it is possible that undetected damaging effects of over-distension and VILI occurred during weaning in both groups using the current ARDSnet protocol.

The application of even low levels of pressure support, combined with large negative inspiratory pressures results in TVs and trans-alveoli pressures that may induce VILI. If spontaneous is allowed the volume (and the trans-alveolar membrane pressure) should be restricted!.

Should we limit spontaneous breathing with neuro-muscular blockade?

Neuromuscular blocking agents (NMBA), when used by expert anaesthetists, provide a useful adjunct to general anaesthesia. However, in the ICU environment the benefits of NMBA and their role in ARDS management remains controversial [34].

Over half a century ago, Beecher and Todd reported outcomes from an analysis of over half a million case reports of patients who had undergone anaesthesia and reported a six fold greater mortality associated with curare use [35]. Their report speculated that curare possessed “inherent toxicity”, a belief that profounded effected NMBA use. During the same era, prototypes of today’s ICU were developed to manage patients stricken by polio, in whom muscle paralysis was the presenting cause rather than the solution to the ventilation problems [34]. The postulated “toxicity” of curare influenced practice for at least the next decade, until refuted in 1961 when Dripps published a series of 6000 cases of anaesthesia involving NMBA, without a single mortality [36].

With time, the inevitable migration of anaesthetic practice to ICUs resulted in NMBA being used in 98 % of North American ICUs. A recent survey of New Zealand ICUs found that 95% of ventilated patients receive at least one dose of NMBA. (Freebairn, unpublished data).

Suggested indications for the use of NMBA in ARDS were to improve oxygen delivery, increase respiratory

synchrony and compliance, and to reduce oxygen consumption. While confirming respiratory compliance changes, we were unable to demonstrate changes in oxygen consumption or delivery with NMBA [37]. Established guidelines recommend NMBAs should be used in an ICU to manage ventilation, and decrease oxygen consumption **only when all other means have been tried without success** [38].

Prolonged routine use of NMBA is not common with only 3 % of ventilated patients receive NMBA after 48 hours.(Freebairn, unpublished data) However, clinicians faced with patients with recalcitrant hypoxemia despite 100% oxygen and elevated PEEP almost invariably resort to heavy sedation and muscle paralysis.

In a recent randomised placebo controlled study in French ICUs, Gannier and colleagues demonstrated a sustained improvement in PaO₂/FiO₂ ratios in a group of ventilated patients with ARDS, managed with a forty eight hour course of NMBA [39]. Surprisingly, little change in the measured parameters occurred until the infusion was completed, but subsequent oxygenation improvement was sustained for at least three days. Wrigge has suggested that insufficient or asynchronous inspiratory muscle activity of non-paralyzed placebo patients resulted in increased oxygen demand and/or mismatching of the distribution of ventilation and pulmonary perfusion, which may have contributed to ongoing arterial hypoxemia [40]. A direct pharmacological effect of cis-atracurium would have a rapid onset, be sustained throughout the infusion and fade away when the infusion ceased. Oxygenation improvement in Gannier’s study is not evident until 48 hours, and is sustained beyond the recovery of neuromuscular function. Why the “hypoxemia produced by asynchrony or increased oxygen consumption” was not evident immediately during placebo infusion, or is why, after the cessation of NMBA, the group receiving active drug did not revert to the same levels as the placebo group is not accounted for in Wrigge’s explanation.

The oxygenation benefit is paralleled by PEEP and plateau pressures improvements. After 48 hours those receiving NMBA had more compliant lungs and appeared to have more functional alveoli than those receiving placebo, signifying less VILI. This may have resulted from decreased localized intrapulmonary damage, or from a reduction or inactivation of circulating mediators. In either case, attenuation of VILI could give rise to improved oxygenation and the potential for improved survival. While the exact mechanism is unclear, but a reduction spontaneous respiration interfering with TVs has been postulated [34]. While ventilation with assist-control occurs under paralysis, there is no opportunity for additional

breaths, and when set correctly, adequate expiratory time is guaranteed. Triggered breaths, even in assist control mode, can stack breaths, delivering TVs prior to complete expiration. As higher respiratory rates during low volume ventilation induce auto-PEEP and breathe stacking, it would not be surprising if spontaneous ventilation exacerbated this problem [41].

Despite Gannier's limited study population the ICU and 28-day mortality differences came close to statistical significance [39]. The trend of absolute mortality reduction of 25% translates to a number needed to treat of only four, and needs to be confirmed in an appropriately powered study. There is immense interest in novel therapeutics for ARDS. A new patented therapeutic providing a 25 % mortality reduction would be coveted, but would likely to be cost significantly more than 48 hours of NMBA.

Gannier's group have also studied patients under similar conditions to their original study and presented that data at the ISICEM meeting 2005, suggesting decreases in inflammatory mediators levels following neuromuscular blockade. We await the formal publication of their data.

Over-distension of alveoli, even at low ventilator driving pressures may be as dangerous as high tidal vol-

ume (TV) controlled ventilation and thus naïve use of unrestricted spontaneous breathing techniques may be detrimental.

Conclusion

Spontaneous breathing in the ventilation management of ARDS remains controversial. While theoretical benefits and some limited experimental and clinical data support APRV use, we await clear evidence of improvement in clinical outcome.

Conversely an argument that the unrestrained use of pressure support and other spontaneous breathing modes may induce VILI is supported by both logical theory and some evidence. Ablating spontaneous breathing for two days with NMBA appears to produce oxygenation benefits, and a trend towards increased survival [34].

Spontaneous ventilation in ARDS remains experimental, and as its naïve uncritical use may be detrimental, its use warrants a properly conducted randomized trial. When used it must be monitored with close supervision, with ongoing attention to limiting tidal volumes and whenever practical with measurement of oesophageal pressures, to reduce the risk of VILI.

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