

# STRATEGIES FOR REDUCING VENTILATOR-INDUCED LUNG INJURY

Driving pressure and the Puritan Bennett™ Ventilator PAV+™ Software

Driving pressure — a measure of the relationship between tidal volume and the effective lung size of the patient — has been revealed as a major predictor of mortality risk.<sup>1</sup> Allowing the patient to control driving pressure through patient-driven modes such as the PAV+™ breath type software may present an alternative to traditional lung-protective ventilation strategies.



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8	GEORGOPOULOS 2016	Georgopoulos D, Xirouchaki N, Tzanakis N, Younes M. Driving pressure during assisted mechanical ventilation: is it controlled by patient brain? <i>Respir Physiol Neurobiol.</i> 2016;228:69–75.
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## Overview

Over the past 20 years, clinicians have focused significant attention on minimizing adverse effects of mechanical ventilation. In attempting to reduce mortality, they have implemented various lung-protective ventilation strategies.<sup>2-4</sup> However, clinical trials have shown inconsistent benefits of these strategies, depending on which ventilation parameters are manipulated.<sup>5-9</sup> A strategy that avoids a tidal volume ( $V_T$ ) that is excessive for the effective lung size and avoids repeated opening and closing of lung units has been demonstrated to reduce mortality.<sup>7</sup> Despite an associated survival benefit, lung-protective ventilation strategies that reduce  $V_T$  may cause air hunger, increasing patient-ventilator asynchrony and thereby not achieving optimal patient outcomes.<sup>10-12</sup> Recently, driving pressure ( $\Delta P$ ) — a measure of the relationship between  $V_T$  and the effective lung size of the patient — has been revealed as a major predictor of mortality risk.<sup>1</sup> Allowing the patient to control  $\Delta P$  through patient-driven modes such as the PAV+™ breath software type may present an alternative to traditional lung-protective ventilation strategies.

## What is ventilator-induced lung injury?

Mechanical ventilation is important to the supportive care of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), yet it can cause additional damage to the lung.<sup>3</sup> Ventilator-induced lung injury (VILI) contributes to mortality and morbidity.<sup>4</sup> The table below defines two important types of VILI.

Types of ventilator-induced lung injury (VILI)	
<b>Volutrauma</b>	Lung damage resulting from overdistention due to excessive $V_T$ . Animal studies have demonstrated that lung stretching caused by excessive volume delivery in relation to lung size and not excessive airway pressure is primarily responsible for VILI. <sup>2,4</sup>
<b>Atelectrauma</b>	Lung damage resulting from shearing forces. Inadequate end-expiratory lung volumes can lead to this kind of injury via repetitive opening and closing of airway units and altered surfactant function. <sup>4</sup>



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## Ventilation strategies to reduce VILI

In the late 1990s, conventional ventilation approaches aimed to use the lowest positive end-expiratory pressure (PEEP) that provided adequate oxygenation, with priority given to maintaining optimal partial pressure of arterial CO<sub>2</sub> and pH.<sup>1,7</sup> V<sub>T</sub> was generally set to 10 to 15 mL per kg body weight.<sup>9</sup> At this time, several clinical trials were designed to test whether reducing V<sub>T</sub> could reduce VILI with an attendant reduction in mortality. These trials produced conflicting results, as shown in Table 1. Modified ventilation strategies (Table 1) included:

- Controlling inspiratory driving pressure while reducing V<sub>T</sub> and maintaining high PEEP<sup>5</sup>
- Limiting end-inspiratory plateau pressure<sup>6</sup>
- Limiting peak inspiratory pressure and V<sub>T</sub><sup>8</sup>
- Limiting end-inspiratory plateau pressure and V<sub>T</sub><sup>9</sup>

**TABLE 1.** Clinical trials of lung-protective ventilation strategies

Trial	Patient population	Ventilation strategy		Mortality (%)		P value
		Conventional	Protective	Conventional	Protective	
Amato 1998 <sup>5</sup>	53 with early ARDS	Lowest possible PEEP, V <sub>T</sub> 12 mL/kg	PEEP above lower inflection point, V <sub>T</sub> <6 mL/kg, driving pressure <20 cmH <sub>2</sub> O above PEEP, pressure-limited modes	70.8% <sup>a</sup>	37.9%	<0.001
Brochard 1998 <sup>6</sup>	116 with ARDS	VT 10 mL/kg or above, close to normal PaCO <sub>2</sub>	V <sub>T</sub> <10 mL/kg, limit plateau pressure to 25 cmH <sub>2</sub> O	37.9% <sup>b</sup>	46.6%	0.38
Stewart 1998 <sup>9</sup>	120 at high risk for ARDS	Peak inspiratory pressure as high as 50 cmH <sub>2</sub> O, V <sub>T</sub> 10 to 15 mL/kg	V <sub>T</sub> 8 mL/kg or less, peak inspiratory pressure 30 cmH <sub>2</sub> O or less	47% <sup>c</sup>	50%	0.72
Brower 1999 <sup>8</sup>	52 with ARDS	V <sub>T</sub> 10 to 12 mL/kg, reduced if inspiratory plateau pressure >55 cm H <sub>2</sub> O	V <sub>T</sub> 5 to 8 mL/kg, keep plateau pressure <30 cmH <sub>2</sub> O	46% <sup>c</sup>	50%	0.61
ARDSnet 2000 <sup>7</sup>	861 with ALI and ARDS	V <sub>T</sub> initially 12 mL/kg, adjusted to maintain plateau pressure between 45 and 55 cmH <sub>2</sub> O	V <sub>T</sub> initially 6 mL/kg, adjust to maintain plateau pressure between 25 and 30 cmH <sub>2</sub> O	39.8% <sup>c</sup>	31.0%	0.007

<sup>a</sup> 28-day mortality, <sup>b</sup> 60-day mortality, <sup>c</sup> in-hospital mortality



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A pivotal study involving over 850 patients led to the currently accepted lung-protective ventilation strategy.<sup>7</sup> This study tested whether reducing  $V_T$  and limiting end-inspiratory plateau pressure would improve clinical outcomes, including mortality before discharge (Table 1).<sup>7</sup> The protective ventilation strategy reduced mortality by 22% ( $p = 0.005$ ) and led to the ARDSnet strategy, in which plateau pressure is  $\leq 30$  cmH<sub>2</sub>O, PEEP is 5 to 15 cmH<sub>2</sub>O, and  $V_T$  is  $\leq 7$  mL/kg ideal body weight.

As shown in Table 1, only the ARDSnet study and the study by Amato et al demonstrated a survival benefit. One reason proposed for this observation is that higher PEEP and lower  $V_T$  were used in both studies and this combination is thought to be protective.<sup>7</sup> In the ARDSnet protocol, higher PEEP was allowed to maintain arterial oxygenation, which resulted in a higher average PEEP value in the low  $V_T$  group. In the study by Amato et al, higher PEEP was used in the protective strategy.<sup>5,7</sup>

More recently, additional clinical trials have investigated the optimal PEEP setting for use with the ARDSnet strategy (Table 2).<sup>3,13-18</sup> In general, higher PEEP settings have been found to improve some clinical endpoints but have no effect on mortality. Using in-hospital mortality as an endpoint, a systematic review of three large trials found evidence for a reduction in mortality with higher PEEP only in the subset of patients with ARDS.<sup>13</sup>

**TABLE 2.** Clinical studies investigating the optimal level of PEEP and in-hospital mortality for use with the ARDSnet strategy

Trial	Patient population	Ventilation strategy		Mortality (%)		P value
		Conventional	Protective	Conventional	Protective	
Brower 2004 <sup>14</sup>	549 with ALI and ARDS	$V_T$ 6 mL/kg, end inspiratory plateau pressure $<30$ cmH <sub>2</sub> O, low PEEP values	$V_T$ 6 mL/kg, end inspiratory plateau pressure $<30$ cmH <sub>2</sub> O, High PEEP values	24.9%	27.5%	0.48
Meade 2008 <sup>3</sup>	983 with ALI	ARDSnet	Plateau pressure $<40$ cmH <sub>2</sub> O, recruitment maneuvers, higher PEEP	36.4% <sup>a</sup>	40.4%	0.19
Mercat 2008 <sup>17</sup>	767 with ALI	ARDSnet PEEP 5 to 9 cmH <sub>2</sub> O	PEEP as high as possible keeping plateau pressure 28 to 30 cmH <sub>2</sub> O	39.0%	35.4%	0.30
Briel 2010 <sup>13</sup>	2299	Low PEEP	High PEEP	35.2%	32.9%	0.25

<sup>a</sup> 28-day mortality, <sup>b</sup> 60-day mortality, <sup>c</sup> in-hospital mortality

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## Lung-protective ventilation strategies may be associated with increased sedative administration, patient-ventilator asynchrony, and patient discomfort

Though the ARDSnet strategy reduces mortality, mortality rates remain high among patients with ALI and ARDS, and VILI still may occur.<sup>19</sup> One contributing factor may be that the ARDSnet strategy often results in a set  $V_T$  that is smaller than what the patient desires.<sup>11</sup> If the patient's breathing effort is not suppressed, the patient may experience air hunger and the potential for increased patient-ventilator asynchrony with double triggering of ventilator breaths.<sup>10,12</sup> In this case, without time in between breaths for exhalation, twice the set  $V_T$  is delivered to the patient. In fact, studies have suggested a risk of alveolar hyperinflation with the ARDSnet protocol.<sup>16</sup> Increased sedation with associated negative effects may be needed to reduce patient breathing drive so as to avoid asynchrony issues.<sup>10,12</sup>

The objectives for mechanical ventilation can be contradictory, allowing for disagreement regarding best ventilation practices. Conventional mechanical ventilation strategies using sedation and analgesia to diminish respiratory drive (passive ventilation) can prevent damage to structural tissues, alveoli, and the diaphragm resulting from a high breathing drive. However, this approach may also result in diaphragm atrophy, referred to as ventilator-induced diaphragmatic dysfunction (VIDD).<sup>20</sup> Providing appropriate assistance to spontaneous breathing can prevent VIDD but may itself result in respiratory muscle weakness.<sup>20</sup> Both promoting and preventing spontaneous breathing have the potential to provide significant benefits, and both may also result in inflammation as well as muscle weakness and wasting.<sup>20</sup> Therefore, further optimization of mechanical ventilation strategies could provide possible further improvements in clinical outcomes.

## Using driving pressure to target tidal volume to the functional size of the lung

Amato et al reanalyzed individual data from more than 3,500 ARDS patients enrolled in nine randomized controlled clinical studies. Their analysis revealed that, for patients who are ventilated passively, controlling  $\Delta P$  so that  $V_T$  is normalized to functional lung size rather than ideal body weight is more strongly associated with survival than controlling  $V_T$  alone.<sup>1</sup> For these patients, a reduction in  $V_T$  increased survival only when associated with a decrease in  $\Delta P$ .<sup>1</sup>

Driving pressure ( $\Delta P$ )	Static end-inspiratory plateau pressure (Pplat) – PEEP or $V_T$ /Respiratory system compliance ( $C_{RS}$ ) ratio
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When patients are ventilated with patient-directed, proportional forms of mechanical ventilation (such as proportional assist ventilation [PAV+™ software]), sedation is limited so the patient's respiratory drive remains intact

and neither  $\Delta P$  or  $V_T$  are set by the caregiver. Instead, the patient's instantaneous muscle activity and intrinsic reflexes — such as the Hering-Breuer inflation reflex, which senses lung stretch and adjusts breathing to protect the lung from overdistension — control ventilation.

Georgopoulos et al hypothesized that when patients are allowed to direct spontaneous breathing (as is the case with the PAV+™ software), feedback mechanisms may naturally act to restrict  $\Delta P$  but not necessarily restrict  $V_T$ .<sup>11</sup> They compared the  $\Delta P$  applied during passive controlled mechanical ventilation (CMV) using the currently accepted lung-protective strategy with the  $\Delta P$  measured when the same patients were ventilated with the PAV+™ software. When patients were switched from CMV to the PAV+™ software, they automatically adjusted their breathing to limit  $\Delta P$ .<sup>11</sup> This result indicates that natural feedback mechanisms can function in these patients, allowing them to optimize  $V_T$  to their own respiratory system compliance.<sup>11</sup> This ability of patients to control  $\Delta P$  and  $V_T$  represents one way in which the PAV+™ software may help reduce VILI.



# AMATO 2015

Amato MB, Meade MO, Slutsky AS, et al. **Driving pressure and survival in the acute respiratory distress syndrome.** *N Engl J Med.* 2015;372(8):747–755.

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## STUDY INFORMATION

PURPOSE	To investigate whether driving pressure ( $\Delta P$ ) is more strongly associated with survival than $V_T$ or PEEP			
STUDY DESIGN	Analysis of data from nine previously published clinical trials that compared ventilation strategies in patients with ARDS			
METHODS	<p>Using data from nine previously conducted randomized clinical trials (a total pooled sample of 3,562 patients), a survival-prediction model was created and refined</p> <ul style="list-style-type: none"> <li>▪ Primary outcome was hospital survival at 60 days</li> <li>▪ Univariate and multivariate analyses were used to identify variables associated with survival</li> <li>▪ Patients with evidence of active breathing were excluded</li> </ul>			
RESULTS	<ul style="list-style-type: none"> <li>▪ <math>\Delta P</math> was the variable most strongly associated with survival</li> <li>▪ Statistical analysis indicated that <math>\Delta P</math> mediated the benefits of other interventions such as reductions in <math>V_T</math> or increases in PEEP (changes in <math>V_T</math> or PEEP were not independently associated with survival)</li> </ul>			
	Survival-prediction model version	Variable	Relative risk (95% CI)	P value
	2	Day 1 $\Delta P$	1.40 (1.30-1.51)	<0.001
		Day 1 $V_T$	1.02 (0.95-1.10)	0.58
3	Day 1 $\Delta P$	1.41 (1.32-1.52)	<0.001	
	Day 1 PEEP	1.03 (0.95-1.11)	0.51	
CONCLUSION	Decreased $\Delta P$ was significantly associated with increased survival. Changes in $V_T$ or PEEP were only beneficial if they were associated with a change in $\Delta P$ .			



# GEORGOPOULOS 2016

Georgopoulos D, Xirouchaki N, Tzanakis N, Younes M. **Driving pressure during assisted mechanical ventilation: is it controlled by patient brain?** *Respir Physiol Neurobiol.* 2016;228:69–75.

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## STUDY INFORMATION

PURPOSE	To determine whether patients control VT or $\Delta P$ when they are switched from passive mechanical ventilation (CMV) to the PAV+™ software		
STUDY DESIGN	Reanalysis of data from the subset of patients (n=108) who were switched from CMV to the PAV+™ software in a previous study (Xirouchaki et al, 2008) <sup>21</sup>		
METHODS	<p>Method: For each patient, <math>\Delta P</math> during the periods the patient was ventilated with CMV and with the PAV+™ software were compared</p> <p>Instrument: PB840 ventilator</p>		
RESULTS	<ul style="list-style-type: none"> <li>▪ Average <math>\Delta P</math> did not differ significantly between the 8 hours during CMV before and the initial 8 hours with the PAV+™ software after the switch from CMV to the PAV+™ software</li> <li>▪ VT and respiratory system compliance (CRS) both differed significantly between the PAV+™ software and CMV (<math>p &lt; 0.0001</math>)</li> <li>▪ When <math>\Delta P</math> was high (<math>\geq 15</math> cmH<sub>2</sub>O) during CMV, patients tended to decrease <math>\Delta P</math> with the PAV+™ software</li> <li>▪ CRS increased with the PAV+™ software, such that <math>V_T</math> increased without changing <math>\Delta P</math></li> </ul>		
		<b>CMV</b>	<b>PAV+™ software</b>
	$\Delta P$ , average (interquartile range), cmH <sub>2</sub> O	10.7 (9.0-12.9)	10.2 (8.1-12.4)
CONCLUSION	Critically ill patients can control $\Delta P$ by adjusting VT to CRS. Feedback mechanisms that protect the lungs from overdistension may be active during modes such as the PAV+™ software.		

# GEORGOPOULOS 2016B

Georgopoulos D, Xirouchaki N, Tzanakis N, Younes M. **Data on respiratory variables in critically ill patients with acute respiratory failure placed on proportional assist ventilation with load adjustable gain factors (PAV+)**. *Data Brief*. 2016;8:484–493.

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## STUDY INFORMATION

PURPOSE	To provide the respiratory variable data set analyzed in Georgopoulos et al, 2016a
STUDY DESIGN	Reanalysis of data from the subset of patients (n=108) who were switched from CMV to the PAV+™ software in a previous study (Xirouchaki et al, 2008) <sup>21</sup>
METHODS	<ul style="list-style-type: none"><li>▪ Data for the following respiratory variables for each patient during CMV and during the PAV+™ software are provided:<ul style="list-style-type: none"><li>– <math>V_T</math></li><li>– <math>\Delta P</math></li><li>– CRS</li><li>– Respiratory system resistance</li><li>– Arterial blood gasses</li></ul></li><li>▪ Data are presented for ARDS and non-ARDS groups</li></ul>
RESULTS	<ul style="list-style-type: none"><li>▪ Data are the same as presented in Georgopoulos 2016a. However, the data for ARDS and non-ARDS patients are presented separately, whereas they were pooled in Georgopoulos 2016a.</li><li>▪ For both ARDS and non-ARDS patients, CRS and VT differed significantly between CMV and the PAV+™ software but <math>\Delta P</math> did not</li><li>▪ For both ARDS and non-ARDS patients, the percent of measurements during which <math>V_T</math> was <math>&lt;7</math> mL/kg or <math>&lt;8</math> mL/kg was significantly less during the PAV+™ software than during CMV (<math>p &lt; 0.0001</math>)</li><li>▪ Across all patients, when <math>\Delta P</math> was <math>\leq 8</math> cmH<sub>2</sub>O during CMV, patients tended to increase <math>\Delta P</math> after the switch to the PAV+™ software (59/65 measurements)</li><li>▪ Across all patients, when <math>\Delta P</math> was <math>\geq 15</math> cmH<sub>2</sub>O during CMV, patients tended to decrease <math>\Delta P</math> after the switch to the PAV+™ software (58/67 measurements)</li></ul>
CONCLUSION	The authors state that the data may encourage future research into feedback mechanisms that may protect the lungs of critically ill patients from VILI. The data may help guide new strategies for mechanical ventilation of critically ill patients.



# NETO 2016

Neto AS, Hemmes SN, Barbas CS, et al. **Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data.** *Lancet Respir Med.* 2016;4(4):272–280.

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## STUDY INFORMATION

PURPOSE	To investigate the relationship between the occurrence of postoperative complications and intraoperative values of $V_T$ , PEEP, and $\Delta P$		
STUDY DESIGN	Meta-analysis of data from 17 previously published randomized controlled clinical trials of protective ventilation during general anesthesia during surgery		
METHODS	Multivariate analysis of data from 17 trials, N=2,250 patients		
RESULTS	<ul style="list-style-type: none"> <li>▪ The effect of PEEP in univariate analysis was not large enough to include PEEP in the multivariate analysis</li> <li>▪ <math>V_T</math> was not significantly associated with development of postoperative pulmonary complications in multivariate analysis</li> <li>▪ Increases of <math>\Delta P</math> were associated with development of postoperative pulmonary complications in multivariate analysis</li> <li>▪ In a mediator analysis, only <math>\Delta P</math> was associated with development of postoperative pulmonary complications (<math>p = 0.027</math>)</li> </ul>		
	Variable	Odds ratio (95% CI)	P value
	$V_T$	1.05 (0.98-1.13)	0.179
	$\Delta P$	1.16 (1.13-1.19)	<0.001
CONCLUSION	During surgery, high intraoperative driving pressure is associated with increased occurrence of postoperative pulmonary complications.		

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