Research Article

High tidal volume ventilation is associated with ventilator-associated pneumonia in acute cervical spinal cord injury

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Context/Objective: Pneumonia is the leading cause of death after acute spinal cord injury (SCI). High tidal volume ventilation (HVTv) is used in SCI rehabilitation centers to overcome hypoventilation while weaning patients from the ventilator. Our objective was to determine if HVTv in the acute post-injury period in SCI patients is associated with lower incidence of ventilator-associated pneumonia (VAP) when compared to patients receiving standard tidal volume ventilation.

Design: Cohort study.

Setting: Red Duke Trauma Institute, University of Texas Health Science Center at Houston, TX, USA.

Participants: Adult Acute Cervical SCI Patients, 2011–2018.

Interventions: HVTv.

Outcome measures: VAP, ventilator dependence at discharge, in-hospital mortality.

Results: Of 181 patients, 85 (47%) developed VAP. HVTv was utilized in 22 (12%) patients. Demographics, apart from age, were similar between patients who received HVTv and standard ventilation; patients were younger in the HVTv group. VAP developed in 68% of patients receiving HVTv and in 44% receiving standard tidal volumes ($P = 0.06$). After adjustment, HVTv was associated with a 1.96 relative risk of VAP development (95% credible interval 1.55–2.17) on Bayesian analysis. These results correlate with a >99% posterior probability that HVTv is associated with increased VAP when compared to standard tidal volumes. HVTv was also associated with increased rates of ventilator dependence.

Conclusions: While limited by sample size and selection bias, our data revealed an association between HVTv and increased VAP. Further investigation into optimal early ventilation settings is needed for SCI patients, who are at a high risk of VAP.

Keywords: Spinal cord injury, High tidal volume ventilation, Ventilator-associated pneumonia

Introduction

Pneumonia is the leading cause of death after acute spinal cord injury (SCI) and is associated with poor neurologic recovery, increased length of stay, and increased mortality.^{1,2} Respiratory complications occur

in 36% to 83% of patients after cervical SCI and are the cause of 50% of deaths in this population.^{3–6} Optimization of respiratory support and early ventilator weaning for patients with acute cervical SCI are vital to mitigate the risk of ventilator-associated pneumonia (VAP). VAP increases the need for prolonged mechanical ventilation and worsens neurologic recovery, which lead to increased long-term ventilator dependence.^{7,8} People with SCI surviving to one-year post injury who are ventilator dependent have approximately

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half the life expectancy of similarly injured individuals who are not ventilator dependent.⁹

Few ventilator management strategies aiming to decrease the duration of ventilator dependence have been evaluated in SCI patients, both in the acute and sub-acute rehabilitation settings. High tidal volume ventilation (HVtV) is used in SCI rehabilitation centers across the United States to overcome hypoventilation while weaning from the ventilator, based on the Consortium for Spinal Cord Medicine Guidelines.¹⁰ The grade C, level V recommendation is based on a single cohort study of 42 patients, by Peterson *et al.*, which found that patients placed on high volume ventilation after admission to a sub-acute rehabilitation center were liberated from the ventilator on average 21 days sooner than those ventilated with lower tidal volumes.¹¹ The benefit of high tidal volume is believed to be due to additional recruitment of distal airways, surfactant production stimulation, and subsequent improvement in oxygenation.¹² Elevated airway pressure is rare with elevated tidal volumes due to loss of muscle tone in these individuals and the subsequent risk of alveolar over-distention is theoretically diminished. Despite the national guidelines supporting widespread use of HVtV, there is limited evidence regarding the safety or effectiveness of HVtV in patients with cervical SCI, particularly in the acute post-injury period.⁹ Furthermore, there is limited evidence regarding the effect of HVtV on VAP after acute SCI, which is particularly hazardous to this patient population. The aim of this study was to evaluate the safety and effectiveness of HVtV in the acute post-injury period for patients with cervical SCI. Based on prior work in the rehabilitation setting, the primary hypothesis was that HVtV is associated with fewer episodes of VAP than ventilation with standard tidal volumes in patients with acute cervical SCI.

Methods

A cohort study of adult (>16 years) trauma patients with acute cervical SCI admitted to a level 1 trauma center from 2011 to 2018 was performed. The acute post-injury period was defined as the index hospitalization after injury. Patients were primarily admitted to one of two units based on associated injuries and spine surgeon preference: the Shock Trauma Intensive Care Unit or the Neurosurgical Intensive Care Unit. Exclusion criteria included: head abbreviated injury scale >5, mechanical ventilation <2 days, and a diagnosis of acute respiratory distress syndrome diagnosed at any time during index hospitalization. Patient demographics including age, sex, race/ethnicity, mechanism

Table 1 Predicted body weight.

Predicted body weight	
Male	$50 + 0.91 \times (\text{height in cm} - 152.4)$
Female	$45.5 + 0.91 \times (\text{height in cm} - 152.4)$

of injury, Injury Severity Score (ISS), weight, height, SCI level, injury completeness, ventilator settings, imaging and culture results, and procedural interventions were collected. HVtV was defined as a median tidal volume >10cc/kg predicted body weight during time on ventilator up to two weeks post-injury. The HVtV was chosen to mirror the institution's spinal cord rehabilitation center's protocol, which titrates the tidal volume from 10cc/kg up to 20cc/kg predicted body weight, in accordance with national guidelines.¹⁰ Predicted body weight was calculated as described in the ARMA Trial (Table 1).¹³ VAP was defined by study personnel according to the 2019 National Trauma Data Bank Dictionary.¹⁴ According to this definition, VAP was assigned if a pneumonia developed on or after the 2nd day of ventilator placement and imaging, signs or symptoms, and laboratory evidence were consistent with pneumonia diagnosis.¹⁴ Standard pneumonia prevention strategies were utilized throughout the study period including, but not limited to, head of bed elevation, daily spontaneous breathing trials, oral care 6 times per day, and subglottic suctioning.¹⁵ Complete spinal cord injury was defined as loss of sensory and motor function beyond the level of injury.¹⁶ This was determined by review of the spine surgeon's documentation.

Statistical analysis

Bayesian analyses were utilized to complement the traditional frequentist analyses in order to maximize the knowledge gained from this study. Bayesian inference applies a *prior*, or an estimated effect distribution based on previous studies, and *likelihood*, which summarizes findings from the present study. The prior and likelihood are combined to generate a *posterior*, or estimated true treatment effect with a credible interval that expresses the magnitude and precision of the treatment effect. The posterior distribution may be utilized to determine the *posterior probability* of a specific effect, such as harm or benefit of the treatment evaluated.¹⁷ Although the point of clinical importance of a treatment may be changed under Bayesian methods, treatment benefit in this study was defined as a posterior relative risk of VAP <1. Relative risks, generated by either Bayesian or frequentist models, are the ratio of the

probability of an outcome occurring in the exposed group to the probability of an outcome occurring in the non-exposed group. A relative risk less than one indicates that patients in the exposed group are at a decreased risk of the outcome of interest, while a relative risk greater than one indicates that patients in the exposed group are at an increased risk of the outcome of interest.

Descriptive analyses were performed to compare baseline demographics and clinical outcomes. Median values with interquartile range were used to describe continuous data and discrete data is reported as a total and frequency. Variables of interest were compared using the Chi-squared test or a Wilcoxon rank-sum test for categorical and continuous variables, respectively. Multivariable frequentist and Bayesian logistic regression were utilized to assess the relationship between VAP and HVtV, while adjusting for potential confounders defined *a priori*: age, ISS, level of injury, trauma type, spinal cord injury completeness, year of care, and offset for length of stay.¹⁸ Neutral, uninformative priors were utilized. Year of care was considered an ordinal variable. Similar models were fit separately for secondary outcomes: ventilator dependence at hospital day 30 or hospital discharge, a composite outcome of pneumonia or mortality, and mortality alone. Secondary models utilized the same variables but were not offset for length of stay. All associations were reported as mean incidence risk ratios with 95% credible intervals and posterior probability of variable association with increased likelihood of outcome. All data analyses were completed using R version 3.53 (R Core Team. 2013. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria).

Results

Between 2011 and 2018, 181 patients met inclusion criteria for this study. Patients were predominantly male and the median age was 47 years and the median BMI was 27 kg/m². VAP developed in 85 (47%) patients. The median days to VAP diagnosis was 7 (IQR 5–12) days.

HVtV was utilized in 22 (12%) patients. The mean tidal volume was 7.6 cc/kg PBW in the standard volume group and 10.8 cc/kg PBW in the HVtV group. The majority of patients received care in the trauma intensive care unit or in the neurosurgical intensive care unit and HVtV was not associated with the location of care. Most patients receiving HVtV presented during 2011 and no patients received HVtV after 2016. On univariate analysis, patients who received

Table 2 Demographic data.

All patients (n = 181)	Standard tidal volume (n = 159)	High tidal volume (n = 22)	P value
Age, years	53 (35–70)	40 (27–51)	0.005
Body mass index (BMI)	27 (24–31)	27 (25–30)	0.77
Year			
2011	19	11	
2012	30	7	
2013	34	1	
2014	19	1	
2015	24	1	<0.001
2016	11	1	
2017	9	0	
2018	13	0	
Male sex	126 (79%)	17 (77%)	1
Race/Ethnicity			
White	89 (56%)	13 (59%)	
Black	34 (21%)	3 (14%)	
Hispanic	27 (17%)	5 (23%)	0.53
Asian	2 (1%)	1 (5%)	
Blunt mechanism of injury	150 (94%)	21 (96%)	1
Critical care location			
Trauma ICU	95 (60%)	11 (50%)	
Neurosurgical ICU	56 (35%)	11 (50%)	0.82
Other	7 (5%)	0	
Injury severity score	26 (17–34)	26 (25–30)	0.49
Complete spinal cord injury (SCI)	61 (38%)	16 (73%)	0.005
SCI level			
C1	11 (7%)	2 (9%)	
C2	26 (16%)	3 (14%)	
C3	24 (15%)	3 (14%)	
C4	33 (21%)	6 (27%)	0.96
C5	42 (26%)	5 (23%)	
C6	18 (11%)	3 (14%)	
C7	5 (3%)	0	
Median tidal volume, cc/kg PBW	7.6 (6.8–8.6)	10.8 (10.2–11.3)	<0.001

Continuous data presented as: median (IQR); ICU – Intensive Care Unit, OR – Operating Room, PBW – predicted body weight.

HVtV were younger and more likely to have a complete SCI (Table 2). Patients who received HVtV were more likely to develop VAP and require a tracheostomy than those who received standard tidal volumes. The median time to tracheostomy was 7 (IQR 5–11) days. All patients received HVtV prior to tracheostomy or VAP diagnosis (Table 3). Hospital-Free Days and Vent-Free Days were similar between groups but patients with HVtV were more likely to be discharged to a Skilled Nursing Facility or to Rehabilitation.

Primary outcome

HVtV was associated with increased risk of VAP on both frequentist and Bayesian analyses. On frequentist analysis, HVtV was associated with an estimated 1.48 increased risk of VAP (95% confidence interval 0.44–

Table 3 Outcome data.

All patients (n = 181)	Standard tidal volume (n = 159)	High tidal volume (n = 22)	P value
Ventilator-associated pneumonia	70 (44%)	15 (68%)	0.06
Days from admission to VAP	7 (5–12)	7 (4–10)	0.45
Tracheostomy	100 (63%)	19 (86%)	0.05
Days from admission to tracheostomy	8 (5–11)	7 (5–9)	0.61
30-Day vent free days	2 (0–9)	1 (0–7)	0.47
30-Day hospital free days	9 (0–15)	12 (2–14)	0.52
Discharge disposition			
Home	22 (14%)	0	0.07
Inpatient rehabilitation	80 (50%)	12 (55%)	
Long-term care facility	20 (13%)	6 (27%)	
Skilled nursing facility	12 (8%)	1 (5%)	
Nursing home	3 (2%)	0	
Hospice	2 (1%)	0	<0.001
Other	1 (1%)	0	
Ventilator dependence at 30 hospital days or hospital discharge	61 (38%)	18 (82%)	
Composite in-hospital mortality or pneumonia	82 (52%)	15 (68%)	0.22
In-hospital mortality	19 (12%)	3 (14%)	1

Continuous data presented as: median (IQR), ICU – Intensive Care Unit.

4.98) (Figure 1). On Bayesian analysis, HVtV was associated with an estimated relative risk of 1.96 (95% credible interval 1.55–2.17) and a >99% posterior probability that HVtV increases VAP. Complete injury, high SCI level, low ISS, older age, and blunt injury mechanism were associated with increased VAP development (Table 4).

Secondary outcomes

The secondary outcome of ventilator dependence at 30 days or hospital discharge occurred in 79 (44%) patients.

Figure 1 Forrest plot of the association between high tidal volume ventilation and primary and secondary outcomes on frequentist analyses.

On frequentist analysis, HVtV was associated with relative risk of 9.98 (95% confidence interval 2.28–42.1) for ventilator dependence at 30 days or hospital discharge (Figure 1). On Bayesian analysis, HVtV was associated with a relative risk of 2.07 (95% credible interval 1.48–2.71) and a posterior probability of >99% that HVtV increases ventilator dependence (Table 4). Higher injury level, complete injury, older age, higher injury severity score, and earlier year of care were associated with ventilator dependence at 30 days or hospital discharge.

The secondary composite outcome of VAP or mortality occurred in 97 (54%) patients. On frequentist analysis, HVtV was associated with an estimated relative risk of 1.40 (95% confidence interval 0.38–5.14) for VAP or mortality (Figure 1). On Bayesian analysis, HVtV was associated with a relative risk of 1.29 (95% credible interval 0.86–1.71) and a posterior probability of 91% that HVtV increases VAP or mortality (Table 4). Complete injury, high SCI level, high ISS, older age, and blunt injury mechanism were also associated with the composite outcome of VAP or mortality.

In-hospital mortality occurred in 22 (19%) patients. Mortality was due to respiratory failure in 23% of cases, sepsis in 18%, cardiac failure in 14%, and withdrawal of mechanical support in 32% of cases. The median time to death was 10 days (IQR 4–12). HVtV was associated with a 2.48 (95% confidence interval 0.24–24.1) relative risk of in-hospital mortality on frequentist analysis (Figure 1). On Bayesian analysis, HVtV was associated with a relative risk of 1.03 (95% credible interval 0.26–2.76) for mortality, and a 52% posterior probability that HVtV increases mortality. Variables associated with increased mortality included high injury level, complete injury, high ISS, older age, blunt mechanism of injury, and earlier year of care (Table 4). On sensitivity analysis applying a threshold of 8cc/kg to define HVtV, there was an imprecise association between HVtV and VAP on multivariable frequentist analysis with a relative risk of 1.04 (95% confidence interval 0.49–2.22).

Discussion

This is the first study to investigate the association between HVtV and increased rates of VAP in the acute post-SCI period. Contrary to the hypothesis, HVtV was found to be associated with increased risk of VAP and decreased likelihood of achieving ventilator independence. While limited by selection bias and sample size, these results question both the safety and effectiveness of HVtV in the acute post-SCI period.

Table 4 Estimated relative risk of primary and secondary outcomes – Bayesian multivariable logistic analyses.

	Primary outcome: ventilator-associated pneumonia		Ventilator dependence at 30 days or hospital discharge		Composite pneumonia or mortality		Mortality	
	Incidence risk ratio (95% credible interval)	PP	Incidence risk ratio (95% credible interval)	PP	Incidence risk ratio (95% credible interval)	PP	Incidence risk ratio (95% credible interval)	PP
HVtV	1.96 (1.55–2.17)	>99%	2.07 (1.48–2.71)	>99%	1.29 (0.86–1.71)	91%	1.03 (0.26–2.76)	52%
Injury level (per each level lower)	1.00 (0.97–1.04)	48%	0.98 (0.89–1.08)	35%	0.99 (0.91–1.07)	37%	0.98 (0.75–1.26)	42%
Complete injury	1.01 (0.94–1.16)	57%	2.81 (1.19–4.09)	>99%	2.02 (1.52–2.69)	>99%	3.22 (1.29–7.17)	>99%
Penetrating mechanism	0.24 (0.02–0.70)	0.2%	1.08 (0.45–1.79)	57%	0.36 (0.07–0.83)	0.4%	0.84 (0.05–2.75)	31%
Age (per 10 years)	1.15 (1.06–1.21)	>99%	1.06 (0.98–1.16)	92%	1.02 (0.95–1.09)	70%	1.99 (1.47–2.85)	>99%
ISS (per 10 points)	0.94 (0.90–0.98)	0.1%	1.16 (1.08–1.22)	>99%	1.09 (1.02–1.15)	99%	1.73 (1.36–2.18)	>99%
Care year (per year)	1.00 (0.97–1.02)	47%	0.91 (0.83–0.99)	1%	0.97 (0.90–1.03)	19%	0.92 (0.74–1.11)	19%

PP – Posterior probability of variable association with increased outcome, HVtV – High tidal volume ventilation, ISS – Injury Severity Score.

Pneumonia prevention is of primary importance for SCI patients. Pneumonia suffered during initial hospitalization for acute SCI is associated with poorer functional recovery and long-term survival when compared to similarly injured individuals who did not develop pneumonia.¹⁹ Similarly, prevalent infections suffered in the acute post-SCI period are associated with lower gains in American Spinal Injury Association (ASIA) motor score,²⁰ and fewer upward ASIA impairment scale (AIS) motor conversions when controlled for known confounders.²¹

Few studies have previously evaluated ventilator mode and weaning protocols as a preventive strategy for VAP in the acute post-SCI setting. Achievement of ventilator independence was associated with decreased incidence of VAP in patients with cervical SCI in a single-center cohort study by Call *et al.*²² To assess the feasibility of achieving ventilator independence by time of discharge, a multicenter observational study was conducted by the Western Trauma Association in 2013.²³ Their study found that 63% of cervical SCI patients achieved ventilator independence by time of discharge. Those who were mechanically ventilated on discharge were more likely to have suffered VAP than those who achieved ventilator independence (81% vs 31%). The authors encouraged routine ventilator weaning in the acute post-SCI period.²³ Similarly, the present study revealed 52% of cervical SCI patients achieved ventilator independence by hospital discharge and a similar proportion of high cervical spine injuries, reaffirming that ventilator weaning is feasible during the

index hospitalization after SCI. These studies suggest that optimization of ventilator weaning and subsequent achievement of ventilator independence is likely to lead to decreased VAP and improved overall outcomes, however this has not been shown in a prospective study.

Contrary to the findings by Peterson *et al.*, HVtV has been found to be unsafe in many patient populations. The Acute Respiratory Distress Syndrome Network published their landmark clinical trial comparing standard (10–15 cc/kg) tidal volumes to lower tidal volumes for patients with acute respiratory distress syndrome (ARDS) in 2000.¹³ Their study showed decreased mortality and increased time off the ventilator with low tidal volumes, resulting in its widespread adoption for patients with ARDS. Few subsequent studies have evaluated tidal volumes in patients without ARDS, such as those included in the present study.^{24–26} In a recent meta-analysis of observational and randomized studies of patients without ARDS, patients receiving low tidal volumes (<8 cc/kg PBW) were less likely to have pulmonary complications than those receiving intermediate (8–10 cc/kg) or high (>10cc/kg) tidal volume ventilation.^{27,28} The present study supports the findings that HVtV may lead to increased susceptibility to pneumonia and/or bacteremia. In experimental studies, lung and blood bacterial count, inflammatory response, and mortality increases with HVtV.^{28–30} These findings may be due to surfactant dysfunction, increased lung permeability, or destruction of epithelial cells resulting in bacterial translocation from the lung into the systemic circulation with HVtV. The results of the present study

suggest that patients with altered respiratory mechanics and physiology due to spinal cord injury may suffer similar consequences of HVtV as patients without spinal cord injury.

The present study adds to the limited knowledge about the acute care of this special patient population who is likely to be cared for by a multi-disciplinary team including, but not limited to, intensivists, traumatologists, neurosurgeons, and physical medicine and rehabilitation specialists. Re-introduction of high tidal volumes into the acute post-SCI period may be harmful to these patients. There was a change in practice demonstrated by the decrease in the use of HVtV in SCI patients at the study institution is likely to be a consequence of mounting evidence of the harms of HVtV in patients without SCI.^{27,31,32} Temporal changes likely contributed to the change in care of the SCI patients, despite limited understanding of the optimal ventilatory support in the acute phase of SCI. Regardless of ventilation type utilized, results of the present study are consistent with prior findings that cervical SCI results in major morbidities including high rates of pneumonia and high mortality. Robust evidence for pneumonia prevention after acute SCI is lacking. Furthermore, the present study included a heterogeneous population of cervical SCI and, while SCI completeness was adjusted for in the analyses, this is an important confounder that may have influenced the findings due to inherent differences in acute loss of the mechanical, neurologic, and immunologic function. Complete and incomplete SCI should be evaluated separately in well-designed clinical trials aiming to establish the optimal respiratory support for this patient population in the acute setting.

This study has several limitations. First, the retrospective cohort design is unable to address the selection bias within the study population. The reasons for a change in practice throughout the study period, with less HVtV being utilized during the later years of the study, are unknown. Second, other ventilation settings were not evaluated in this study, but may play an important role in the optimization of respiratory support in the acute SCI setting. Further evaluation of other parameters, such as plateau pressure and positive end expiratory pressure, is needed. Third, patients were not stratified by SCI severity beyond complete injury and therefore the altered respiratory physiology due to injury was likely to be heterogeneous among patients. Formal ASIA evaluation was not completed for most patients and therefore this was not utilized as a variable in assessment. Finally, long-term data of functional and survival outcomes were unavailable, but are of primary importance in this patient population.

Conclusion

This is the first study to evaluate the association between HVtV and VAP in the acute post-SCI period. Our data suggested an association between HVtV and increased incidence of VAP in acute cervical SCI. Further investigation into optimal early ventilation settings is needed for SCI patients, who are at a high risk of VAP.

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Conflicts of interest The authors report no conflicts of interest.

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