ABSTRACT

Background: Inadvertent hyperventilation is associated with poor outcomes from traumatic brain injury (TBI). Hypocapnic cerebral vasoconstriction is well described and causes an immediate and profound decrease in cerebral perfusion. The hemodynamic effects of positive-pressure ventilation (PPV) remain incompletely understood but may be equally important, particularly in the hypovolemic patient with TBI. Objective: Preliminary report on the application of a previously described mathematical model of perfusion and ventilation to prehospital data to predict intrathoracic pressure. Methods: Ventilation data from 108 TBI patients (76 ground transported, 32 helicopter transported) were used for this analysis. Ventilation rate (VR) and end-tidal carbon dioxide (PetCO2) values were used to estimate tidal volume (VT). The values for VR and estimated VT were then applied to a previously described mathematical model of perfusion and ventilation. This model allows input of various lung parameters to define a pressure–volume relationship, then derives mean intrathoracic pressure (MITP). Results: A total of 10,647 measurements were included from the 108 TBI patients, representing about 13 minutes of ventilation per patient. Mean VR values were higher for ground patients versus air patients (21.6 vs. 19.7 breaths/min; p < 0.01). Estimated VT values were similar for ground and air patients (399 mL vs. 392 mL; p = NS) in the fixed model but not the variable (636 vs. 688 mL, respectively; p < 0.01). Mean PetCO2 values were lower for ground versus air patients (30.6 vs. 33.8 mmHg; p < 0.01). Predicted MITP values were higher for ground versus air patients, assuming either fixed (9.0 vs. 8.1 mmHg; p < 0.01) or variable (10.9 vs. 9.7 mmHg; p < 0.01) PaCO2–PetCO2 differences. Conclusions: Predicted MITP values increased with ventilation rates. Future studies to externally validate this model are warranted. Key words: Prehospital; ventilation; Traumatic Brain Injury (TBI); mathematical modeling

INTRODUCTION

The contributions of ventilation to resuscitation outcomes are being increasingly recognized as important. Inadvertent hyperventilation is both common and associated with adverse outcomes from perfusion-sensitive conditions, such as cardiopulmonary arrest and traumatic brain injury (TBI).1,2 In an arrest state, the impact of interrupting chest compressions to provide ventilations with an unprotected airway is well described.3,4 The impact of positive-pressure ventilation (PPV) and the resultant rise in intrathoracic pressure has been recognized as an important contributor, particularly given the tendency of rescuers to hyperventilate during critical resuscitation.5,6

In the TBI population, the impact of hypocapnia on cerebral perfusion is well documented, and inadvertent hyperventilation as reflected by low end-tidal carbon dioxide (PetCO2) or arrival pCO2 values is associated with increased mortality.7–9 The hemodynamic effects of PPV in the perfusing patient remain incompletely understood. Furthermore, the impact of excessively fast ventilation rates, independent of the effect on CO2 levels, is not well studied.

We recently derived a mathematical model to predict mean intrathoracic pressure (MITP) with various ventilation strategies during normo- and hypoperfusion states.10 Here we apply physiological data collected during two prior investigations to this mathematical model to explore the possible hemodynamic impact of
ventilation performed by paramedics and air medical personnel in TBI patients. We hypothesized that predicted MITP values would be excessive, driven largely by ventilation rates that are too high, particularly in providers less experienced with use of capnometry to guide ventilation.

**METHODS**

**Design**

This was a retrospective observational analysis using prospectively collected data from two prior studies. Waiver of informed consent was granted by our investigational review board.

**Setting**

Physiological data were collected prospectively as part of two previous studies. The first was the San Diego Paramedic Rapid Sequence Intubation (RSI) Trial, in which paramedics used succinylcholine to facilitate ETI in severe TBI patients. Patients were enrolled from 1998 through 2002, with a subset of these undergoing PetCO2 monitoring using hand held oximeter-capnometer devices (Tidal Wave Sp, Novametrix Medical Systems, Wallingford, CT).11 The second study prospectively enrolled severe TBI patients undergoing RSI by Southern California air medical crews in 2004.12 Physiological data were exported from the identical oximeter-capnometer devices for analysis.

**Protocols**

Identical protocols for use of oximeter-capnometers were used in both studies. All TBI patients undergoing prehospital RSI were eligible. Oximeter-capnometer devices were placed immediately upon initiation of the RSI protocol. Preoxygenation was performed using a nonrebreather oxygen mask. Midazolam and succinylcholine were administered prior to laryngoscopy. Capnometry was initiated following intubation for confirmation of ET placement and to guide ventilation. In accordance to protocol, a target PetCO2 value above 30 mmHg was targeted for both studies, as PetCO2 and PaCO2 values below 30 mmHg are associated with decreased cerebral perfusion and poor outcomes.1, 8, 13–15 Following delivery of the patient, crews exported the oximeter-capnometer data file for analysis. This included pulse oximetry (SpO2), heart rate (HR), PetCO2 values, and ventilation rate (VR). The sampling frequency was fixed at 8 seconds.

**FIGURE 1.** Distribution of ventilation rates (VR) and end tidal carbon dioxide (PetCO2) values in air medical and ground transport patients. Mean VR values were lower in air medical patients ($p < 0.01$), and mean PetCO2 values were higher in air medical patients ($p < 0.01$).
Data Analysis

The primary objective of this analysis was to apply a mathematical model of ventilation and perfusion to predict MITP during prehospital ventilation following ETI. The previously described mathematical model uses a standard human lung pressure–volume curve to estimate intrathoracic pressure based on input of the following variables: VT, VR, inspiratory time (i), and positive end-expiratory pressure (PEEP). The following MITP formula was used:

\[ \text{MITP} = (\text{VR} \cdot (\text{PPlat} - \text{PEEP}) \cdot (2i + e)/120) + \text{PEEP} \]

Plateau pressure (PPlat) was calculated as a function of volume from PEEP added to the tidal volume (VT). Various intrinsic lung characteristics can also be manipulated to simulate particular disease states. However, standard parameters were utilized for this analysis. As stated, the predictive intrathoracic pressure formula requires input of VR and VT, which was calculated using the following formula previously described by Davis and Davis in greater detail:

\[ V_T = V / \text{VR} \]

where \( V \) is minute ventilation. The value for \( V \) was estimated from the following formula:

\[ V = 6,000 \times 40 / \text{PaCO}_2 \]

where \( \text{PaCO}_2 \) is the arterial carbon dioxide value, 40 mmHg represents a normal arterial CO2 (\( \text{PaCO}_2 \)) value, and 6,000 mL represents normal minute ventilation. The value for \( \text{PaCO}_2 \) was calculated from the formula:

\[ \text{PaCO}_2 = \text{PetCO}_2 + D \]

where \( D \) represents the arterial-to-end-tidal CO2 gradient. The value for \( D \) was estimated using two

**FIGURE 2.** Estimated values for tidal volume (VT) assuming both fixed and variable arterial carbon dioxide-end tidal carbon dioxide (\( \text{PaCO}_2 - \text{PetCO}_2 \)) differences. Estimated VT values assuming a fixed difference were not different between groups (\( p = 0.072 \)). Estimated VT values assuming variable differences were lower for air medical patient (\( p < 0.01 \)).
strategies. The first assumed a constant value of 4 mmHg based on established norms. The second strategy assumed an increasing value with higher VR values using the following equation:

\[ D = 40 - 40\times(V_T - 150)/V_T \]

where \( V_T \) represents tidal volume for various VR values, assuming a \( V = 6,000 \text{ mL} \). This equation accounts for the increasing proportion of dead space ventilation with faster ventilation rates. These two strategies are displayed in Figure 2. Reasoning behind the use of two equations is based on the desire to compare established normal gradients against values affected by changes in ventilation rate, which have been previously well described to affect outcome.\(^1\) Ultimately, this allowed a \( V_T \) value to be estimated for every data point using VR and PetCO\(_2\).

Polynomial regression was then used to generate a best-fit equation describing the relationship between VR and \( V_T \) with “typical” ventilation for both air medical personnel and ground paramedics during their respective study periods. These equations were used to generate “typical” \( V_T \) values through a range of values for VR. These \( V_T \) values were then input into the previously described mathematical model to generate predicted mean intrathoracic pressure values at various VR values for both air medical and ground personnel. The distributions of VR, PetCO\(_2\), estimated \( V_T \), and MITP were presented graphically for both air medical and ground paramedic patients. In addition, air medical and ground paramedic patients were compared with regard to recorded PetCO\(_2\) and VR values as well as estimated values for \( V_T \) and MITP using Student’s \( t \)-test. StatsDirect (StatsDirect Software, Ashwell, UK) was used for all statistical calculations.

**Figure 3.** Predicted mean intrathoracic pressure (MITP) values for air medical and ground paramedic patients. Predicted MITP values were lower for air medical patients assuming either fixed (8.1 vs. 9.0 mmHg, \( p < 0.01 \)) or variable (9.7 vs. 10.9 mmHg, \( p < 0.01 \)) PaCO\(_2\) – PetCO\(_2\) differences.
Significance was assumed for a $p$-value less than 0.05.

**RESULTS**

Physiological data from 76 patients transported by ground paramedics with a total of 6,284 data points and 32 patients transported by air medical crews with 4,363 data points were included in this analysis. This represented a mean monitoring duration of 11 minutes for ground paramedic patients and 18 minutes for air medical patients.

The distribution of VR and PetCO$_2$ values are displayed in Figure 1. Mean VR values were lower in air medical patients (19.7 vs. 21.6 breaths/min, $p < 0.01$), and mean PetCO$_2$ values were higher in air medical patients (33.8 vs. 30.6 mmHg, $p < 0.01$). Estimated values for $V_T$ assuming both fixed and variable PaCO$_2$–PetCO$_2$ differences for air medical and ground paramedic patients are displayed in Figure 2. Mean estimated $V_T$ values assuming a fixed PaCO$_2$–PetCO$_2$ difference were not different between air medical and ground paramedic patients (392 vs. 399 mL, $p = 0.072$). Mean estimated $V_T$ values assuming a variable PaCO$_2$–PetCO$_2$ difference were lower for air medical versus ground paramedic patients (636 vs. 688 mL, $p < 0.01$). Predicted MITP values for air medical and ground paramedic patients are displayed in Figure 3. Predicted MITP values were lower for air medical versus ground patients assuming either fixed (8.1 vs. 9.0 mmHg, $p < 0.01$) or variable (9.7 vs. 10.9 mmHg, $p < 0.01$) PaCO$_2$–PetCO$_2$ differences.

Polynomial regression curves modeling VR against estimated $V_T$ for ground paramedic and air medical patients are displayed in Figure 4. Polynomial regression curves modeling VR against predicted MITP values for ground paramedic and air medical patients are displayed in Figure 5.

**DISCUSSION**

The harmful effects of hypocapnia on outcome from brain injury are well described, with both PetCO$_2$ and PaCO$_2$ values below 30 mmHg associated with decreased cerebral perfusion and worsening outcomes.$^{1-8}$ Current guidelines by the Brain Trauma Foundation’s Prehospital Severe TBI guidelines recommend...
FIGURE 5. Polynomial regression curves modeling ventilation rate (VR) against predicted mean intrathoracic pressure (MITP) values for ground paramedic and air medical patients assuming both fixed and variable arterial carbon dioxide- end tidal carbon dioxide (PaCO₂ – PetCO₂) gradients.

maintaining normocarbia (EtCO₂ 35–40 mmHg), and avoid hyperventilation (EtCO₂ < 35 mmHg) unless the patient shows signs of cerebral herniation. However, despite previous descriptions of a high prevalence in prehospital hypocapnia, current rates of adherence to most recent guidelines in various prehospital systems are not clear. Our preliminary report on historical data demonstrated mean PetCO₂ values that were both lower than current recommendations, however, lower VR appeared to be associated with values closer to current capnography guidelines (33.8 vs. 30.6 mmHg, p < 0.01) and lower MITP values in both the fixed and variable models. Although preliminary, these data may help define the hemodynamic effects of PPV have in perfusing patients. Currently, the relative hemodynamic effects of various combinations of VT and VR are virtually unknown. Most current data are derived from cardiac arrest models, in which excessive ventilation rates have been demonstrated to raise intrathoracic pressure and interfere with venous return and cardiac output.

Hypothesis generation based on our results has possibly important implications for outcome quantification in future studies. In the hemodynamically unstable patient in whom PetCO₂ values may be lower due to perfusion limitations, the effect and importance of ventilation rate on outcome may be better understood rather than the sole focus on the PetCO₂ value itself, which may be unreliable. This preliminary report represents the input of actual prehospital data into...
our mathematical models. While this does not validate the accuracy of the predicted MITP values, it is notable that these are almost identical to the values measured in animal models of hemorrhagic shock and cardiopulmonary arrest.\(^5\)\(^9\) It is important to note that we assumed normal lung characteristics. To account for the inability to measure PaCO\(_2\) values in the field, we created two models to predict the PaCO\(_2\)–PetCO\(_2\) difference. One in which this difference was fixed and the other in which it varied based on VR. On one hand, trauma patients are generally healthy and free of pre-existing pulmonary disease. However, the potential for chest wall injury, contusion, and pneumothorax and the possibility of aspiration in TBI patients may result in a less compliant lung profile. This could possibly further amplify our predicted hemodynamic effects of PPV by creating a faster rise in pressure for a given \(V_T\).

There are several important limitations to this study. First, this is a retrospective observational report of archived data originally obtained from two separate previous studies.\(^11\)\(^12\) These data were utilized for the purpose of convenient representation of two separate EMS systems for the purpose of preliminary mathematical model analysis. This original mathematical model remains to be externally validated, although it is reassuring that the MITP values predicted here were nearly identical to those measured in animal models of hemorrhagic shock and cardiopulmonary arrest.\(^1\) As discussed above, we assumed normal lung physiology, which may not have been true in all patients. In addition, we used derived mathematical equations to predict \(V_T\) based on assumptions regarding normal physiology. We did attempt to adjust for the decreased metabolic demands of a patient having undergone RSI, which was true for both air medical and ground paramedic patients. We did not attempt to account for the impact of hypoperfusion on the PaCO\(_2\)–PetCO\(_2\) difference. While this CO\(_2\) gradient is heavily influenced by pulmonary blood flow and \(V/Q\) mismatches, the vast majority of patients in this study did not have extra axial injuries and were hemodynamically stable. We attempted to account for the possibility of either fixed or variable PaCO\(_2\)–PetCO\(_2\) differences but could not be certain as to which is more accurate. Thus, it is reassuring that the final curves (Figure 5) showed relatively minor differences between the two assumptions. Finally, our mathematical models did not take into account Boyle’s law of pressure with altitude in the air medical cohort. Although pressures would, in theory, vary with altitude differences, the low altitudes associated with our flights would have a negligible effect on MITP.

**CONCLUSIONS**

Our preliminary report on retrospective data using a novel mathematical model demonstrated that the use of PPV with high respiration rates without the proper adjustments to tidal volume was associated with elevated MITP in two separate EMS systems. Further study should be done to externally validate this model in a larger multicenter prospective analysis. This model has potential implications for the education and clinical practice of prehospital providers.

**References**


