The Impact of Hypoxia and Hyperventilation on Outcome after Paramedic Rapid Sequence Intubation of Severely Head-Injured Patients

Daniel P. Davis, MD, James V. Dunford, MD, Jennifer C. Poste, Mel Ochs, MD, Troy Holbrook, PhD, Dale Fortlage, BA, Michael J. Size, MD, Frank Kennedy, MD, and David B. Hoyt, MD

Background: **An increase in mortality has been documented in association with paramedic rapid sequence intubation (RSI) of severely head-injured patients. This analysis explores the impact of hypoxia and hyperventilation on outcome.**

Methods: **Adult severely head-injured patients (Glasgow Coma Scale score of 3–8) unable to be intubated without neuromuscular blockade underwent paramedic RSI using midazolam and succinylcholine; rocuronium was administered after confirmation of tube position. Standard ventilation parameters were used for most patients; however, one agency instituted use of digital end-tidal carbon dioxide ($ETCO_2$) and oxygen saturation (Spo_2) monitoring during the trial. Each patient undergoing digital $ETCO_2$/Spo_2 monitoring was matched to three historical nonintubated controls on the basis of age, gender, mechanism, and Abbreviated Injury Scale scores for each of six body regions. Logistic regression was used to explore the impact of oxygen desaturation during laryngoscopy and postintubation hypocapnia and hypoxia on outcome. The relationship between hypocapnia and ventilatory rate was explored using linear regression and univariate analysis. In addition, trial patients and controls were compared with regard to mortality and the incidence of "good outcomes" using an odds ratio analysis.**

Results: **Of the 426 trial patients, a total of 59 had complete $ETCO_2$/Spo_2 monitoring data; these were matched to 177 controls. Logistic regression revealed an association between the lowest $ETCO_2$ value and final $ETCO_2$ value and mortality. Matched-controls analysis confirmed an association between hypocapnia and mortality. A statistically significant association between ventilatory rate and $ETCO_2$ value was observed ($r = -0.13$, $p < 0.0001$); the median ventilatory rate associated with the lowest recorded $ETCO_2$ value was significantly higher than for all other $ETCO_2$ values (27 mm Hg vs. 19 mm Hg, $p < 0.0001$). In addition, profound desaturations during RSI and hypoxia after intubation were associated with higher mortality than matched controls. Overall mortality was 41% for trial patients versus 22% for matched controls (odds ratio, 2.51; 95% confidence interval, 1.33–4.72; $p = 0.004$).**

Conclusions: **Hyperventilation and severe hypoxia during paramedic RSI are associated with an increase in mortality.**

Key Words: **Hypoxia, Hyperventilation, Outcome, Paramedic rapid sequence intubation, Severely head-injured patients.**

J Trauma. 2004;57:1–10.

The role of secondary insults, including hypoxia and hypotension, in traumatic brain injury is well established, with multiple investigators documenting their association with increased mortality.[1–4] Unfortunately, many patients cannot be easily intubated without the use of medications because of intact airway reflexes and inadequate jaw muscle relaxation.[5–7] This has led to the institution of aggressive prehospital airway protocols, including the use of neuromuscular blockers by aeromedical crews and select paramedic agencies.[8,9] It is clear that the use of these agents as part of rapid sequence intubation (RSI) protocols leads to an increase in intubation success; however, the ultimate effect on outcome is unknown.[6,7,10–13]

Our own experience with paramedic RSI includes a dramatic increase in the intubation success rates for head-injured patients with a Glasgow Coma Scale (GCS) score of 8 or less and an airway success rate of 99%, including 84% orotracheal intubations and 15% using the Combitube (The Kendall Company, Mansfield, MA).[7,14] The initial outcomes analysis, however, revealed an increase in mortality for RSI patients versus matched, nonintubated controls from the same prehospital system.[15] The challenge now exists to determine the cause of this mortality increase. The present study explores the impact of hypoxia and hypocapnia on outcome in patients undergoing RSI for severe traumatic brain injury. In addition, the relationship between hypocapnia and ventilatory rate is determined.

PATIENTS AND METHODS

Design

The San Diego Paramedic RSI Trial prospectively enrolled patients from the entire county; this analysis focuses on a subset of patients undergoing more intensive monitoring.

Submitted for publication October 17, 2003.
Accepted for publication March 18, 2004.

From the Departments of Emergency Medicine (D.D., J.V.D., J.C.P.) and Surgery, Division of Trauma (T.H., D.F., D.H.), Scripps Mercy Hospital (M.S.), Sharp Memorial Hospital (F.K.), and San Diego County Emergency Medical Services (M.O.), San Diego, California.
Presented at the 62nd Annual Meeting of the American Association for the Surgery of Trauma, September 11–13, 2003, Minneapolis, Minnesota.
Address for reprints: Daniel Davis, MD, Department of Emergency Medicine, University of California, San Diego, 200 West Arbor Drive, Suite 8676, San Diego, CA 92103-8676; email: davismed@cox.net.

DOI: 10.1097/01.TA.0000135503.71684.C8

These patients were matched to historical nonintubated controls from the same prehospital system. The enrollment period for this analysis was from November 1998 through April 2002, representing the entire duration of the trial. Waiver of consent was granted by the California State EMS Authority and from the investigational review board for each participating institution.

Setting and Prehospital System

San Diego County has a population of approximately 3 million and an area of 4,261 square miles. Advanced life support (ALS) is provided by 12 different agencies, with all but one agency participating in the trial. Approximately 30% of the over 100,000 transports each year are related to major or minor trauma. Five designated adult trauma centers receive all major trauma victims. Participating paramedics attended an 8-hour training course to learn the RSI procedure and medications, GCS scoring, and ventilation procedures.

The city of San Diego has a population of 1.3 million residing in an area of approximately 400 square miles. The city ALS provider enrolled approximately one third of the trial patients. Midway through the trial, this agency instituted the use of continuous recording handheld oximeter-capnometer devices on all transport units. This analysis focuses on the subgroup of trial patients undergoing more intensive monitoring with these devices.

Subjects

The San Diego Paramedic RSI Trial targeted adult major trauma victims with severe traumatic brain injury. Inclusion criteria were as follows: apparent age 18 years or older, major trauma victim according to county protocols, suspected head injury by mechanism or physical examination findings, GCS score of 3 to 8, and estimated time for transport to the resuscitation suite 10 minutes or greater. Paramedics attempted intubation without RSI medications; if this was unsuccessful because of a clenched jaw or intact airway reflexes, patients were enrolled in the trial. Exclusion criteria included ongoing cardiopulmonary resuscitation before administration of RSI medications or the inability to achieve intravenous access.

Interventions

Trial patients were preoxygenated for a minimum of 60 seconds using a nonrebreather mask before administration of RSI medications; bag-valve-mask ventilations were instituted if oxygen saturation (Spo_2) remained below 95%. Midazolam and succinylcholine were administered before laryngoscopy; rocuronium was administered to maintain paralysis during transport after confirmation of tube position. A simplified, weight-stratification dosing system was used (Table 1). The Combitube was used as a salvage airway device, with CTI mandated after a maximum of three unsuccessful orotracheal intubation (OTI) attempts. If all intubation attempts were unsuccessful, further laryngoscopy attempts were abandoned and bag-valve-mask ventilation performed until spontaneous respirations resumed. Paramedics were taught standard ventilation parameters of 12 breaths/min and a tidal volume of 800 mL; practice with a stopwatch and spirometer was incorporated into the training session.

During the second year of the trial, the San Diego City ALS provider instituted the use of continuous recording handheld oximeter-capnometer devices. The Novametrix Tidal Wave Model 710 (Tidal Wave, Novametrix Medical Systems, Inc., Wallingford, CT) is a handheld in-line oximeter-capnometer with a finger clip Spo_2 sensor and single-use infrared end-tidal carbon dioxide ($ETCO_2$) adaptor. The device records Spo_2, $ETCO_2$, heart rate, and ventilatory rate at 8-second intervals. These data can be downloaded at a later time for analysis. Paramedics from this agency were instructed to adjust ventilation parameters to target an $ETCO_2$ value of 30 to 35 mm Hg.

Data Collection

Data for every trauma patient meeting Major Trauma Outcome Study criteria are entered into a county trauma registry. In addition, a field worksheet served as both a protocol guide and a data collection tool for RSI trial patients, with one of the principal investigators paged immediately after delivery of each patient for a 15-minute telephone debriefing to record prehospital data and confirm proper GCS score calculation. Data from the oximeter-capnometer devices were exported to an Excel (Microsoft Corp., Redmond, WA) spreadsheet for further analysis.

Statistical Analysis

The primary objective for this analysis was to determine the impact of hypoxia and hypocapnia on outcome after paramedic RSI of severely head-injured patients. Patients were excluded from this analysis for the following: inability

Table 1 Rapid Sequence Intubation Medication Protocols Used during the Trial[a]

	Small, 80–140 lb (35–63 kg)	Average, 141–225 lb (63–100 kg)	Large, >225 lb (>100 kg)
Midazolam	2 mg	2.5 mg	3.0 mg
Succinylcholine	4 ml (80 mg)	6 ml (120 mg)	8 ml (160 mg)
Rocuronium	4 ml (40 mg)	6 ml (60 mg)	8 ml (80 mg)
Morphine	2 mg every 10 min for "stress response" (SBP > 140 mm Hg, HR > 100 beats/min)		

SBP, systolic blood pressure.

[a] This simplified dosing strategy allowed for a constant volume of paralytic medication for patients in a given weight stratification.

to be intubated (OTI or CTI) by prehospital personnel after administration of RSI mediations; failure to fulfill Major Trauma Outcome Study criteria; Head/Neck Abbreviated Injury Scale (AIS) score less than 2 or defined by a neck injury; death before admission or in the resuscitation suite within 30 minutes of arrival; and incomplete or inadequate oximeter-capnometer data.

Logistic regression was used to explore the relationship between hypoxia and hypocapnia on outcome, controlling for age, gender, Head/Neck AIS score, Chest AIS score, Abdomen AIS score, and mechanism of injury. Adjusted odds ratios were calculated for the following oximeter-capnometer variables: lowest preintubation Spo_2 recorded; length of desaturation, defined as the duration of preintubation Spo_2 below 90%; lowest postintubation Spo_2 recorded; lowest $ETCO_2$ value recorded; and final $ETCO_2$ recorded (Fig. 1).

The relationship between hypocapnia and ventilatory rate was explored using both logistic regression and univariate analysis. Linear regression was used to determine the association between recorded $ETCO_2$ values and ventilatory rate. Data from the first 90 seconds after intubation were excluded to allow for an equilibration period; these data were felt to reflect the duration of apnea during laryngoscopy rather than the effect of ventilations after intubation. To control for variability in tidal volume between different paramedics, the changes in $ETCO_2$ and ventilatory rate from the first included value were used for analysis. In addition, the mean and median ventilatory rate values recorded at the time of the lowest documented $ETCO_2$ were compared with all other recorded ventilatory rate values using parametric and nonparametric statistics.

The impact of hypoxia and hypocapnia on outcome was also explored using an odds ratio analysis. Each RSI patient was matched to three nonintubated, historical controls from the county trauma registry using the following criteria: age, sex, mechanism of injury, trauma center, Injury Severity Score, Head/Neck AIS score, Face AIS score, Chest AIS score, Abdomen AIS score, Extremities AIS score, and Skin AIS score. Controls were excluded for death before admission or in the resuscitation suite within 30 minutes of arrival and if the Head/Neck AIS score was defined by a neck injury. Matching was performed independent of previous analyses by a single investigator blinded to outcome. For each of the variables explored in the logistic regression analysis, trial patients were stratified into three approximately equal groups, with odds ratios used to quantify the relative mortality difference between trial patients and their matched controls. Parametric and nonparametric statistics were also used when appropriate to compare trial patients and controls with regard to matching parameters and other clinical variables. Statistical significance was attributed to a value of $p < 0.05$. Statistical calculations were performed using StatsDirect (StatsDirect Software, Inc., Ashwell, UK).

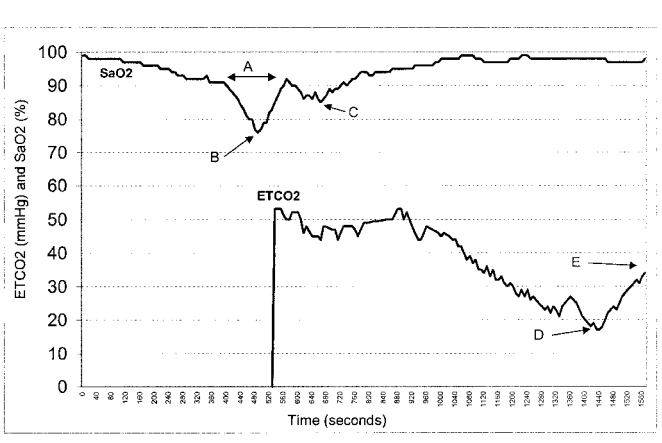

Fig. 1. *Outcome variables used in logistic regression analysis included duration of preintubation Spo_2 below 90% (*A*); lowest preintubation Spo_2 recorded (*B*), lowest postintubation Spo_2 recorded (*C*), lowest $ETCO_2$ value (*D*), and final $ETCO_2$ value (*E*).*

RESULTS

A total of 426 patients were enrolled in the trial; two of these were intubated before paramedic contact but received midazolam and rocuronium for paralysis during transport. In addition, three patients did not receive succinylcholine, and another received a tenth of the protocol dose; none of these achieved appropriate relaxation for intubation. A total of 355 of the remaining 420 patients (84.5%) underwent successful OTI, and 58 (13.8%) underwent successful CTI. The San Diego City ALS provider enrolled 152 of the 426 trial patients (36%). Continuous oximetry-capnometry was introduced by this agency in March 2000, with 59 patients meeting inclusion criteria for this analysis. An additional 43 patients were transported after March 2000 but were excluded for the following reasons: oximeter-capnometer device not used (n = 12); detached Spo_2 monitor during RSI procedure (n = 16); dead battery (n = 8); and corrupt data (n = 7). Of the 43 patients transported by San Diego City ALS providers after institution of oximeter-capnometer devices, 38 would have met inclusion criteria for this analysis; these patients were similar to those included in this analysis with regard to demographics, injury severity, and clinical course (Table 2).

Table 3 displays results from the logistic regression analysis, exploring the impact of various pre- and postintubation parameters on mortality after adjusting for age, gender, Head/Neck AIS score, Chest AIS score, Abdomen AIS score, and mechanism of injury. A statistically significant effect of lowest and final $ETCO_2$ on mortality was observed. A statistically significant association was observed with regard to the changes in $ETCO_2$ and ventilatory rate values from baseline ($r = -0.13$, $p < 0.0001$). This relationship is displayed graphically in Figure 2. In addition, the mean and median ventilatory rate values recorded in association with the lowest observed $ETCO_2$ were significantly higher than all other ventilatory rate values (mean, 28.8 vs. 20.6 mm Hg, $p < 0.0001$; median, 27 vs. 19 mm Hg, $p < 0.0001$). This is

Table 2 Comparison between Patients Meeting Inclusion Criteria for This Analysis in Whom Oximeter-Capnometer Devices Were Used (n = 59) vs. Those in Whom the Devices Were Not Used (n = 38)

Parameter	RSI	Controls	*p* Value
Demographics			
Age (years)	38	31	0.042
Male sex (%)	83	84	0.852
Blunt mechanism of injury (%)	86	90	0.636
Prehospital course			
GCS score	5.0	4.8	0.573
RSI performed on scene (%)	59	71	0.216
Number of intubation attempts	1.6	1.5	0.744
Endotracheal intubation (%)	88	87	0.875
Abbreviated Injury Scale scores (mean values)			
Head/Neck	3.9	3.6	0.178
Face	0.5	0.5	0.858
Chest	1.2	1.0	0.604
Abdomen	0.5	0.8	0.334
Extremities	0.8	1.0	0.549
Skin	0.8	0.9	0.607
ISS	26.6	25.4	0.694
Arrival parameters			
SBP (mm Hg)	135	130	0.480
pH	7.34	7.34	0.898
Po_2 (mm Hg)	299	277	0.509
Pco_2 (mm Hg)	38.2	33.8	0.073
Base deficit	−4.9	−3.4	0.346
Serum ethanol (mg/dL)	107	191	0.090
Hospital course			
Days in ICU	7.0	6.4	0.772
Days in hospital	10.4	13.7	0.384
Mortality (%)	41	32	0.332
Good outcome (%)	41	50	0.406

ISS, Injury Severity Scale; SBP, systolic blood pressure; ICU, intensive care unit.

displayed graphically in Figure 3. These data suggest that the observed hypocapnia was a result of excessively high ventilatory rates.

Table 4 displays data regarding demographics, mechanism of injury, and matching parameters for trial patients (n = 59) and their matched controls (n = 177). The only statistically significant difference between the groups was for Skin AIS score, with trial patients having lower values than controls (0.80 vs. 1.04); this likely had little clinical significance. Table 5 displays values for arrival systolic blood pressure, arterial blood gas data, and serum ethanol. Of note, Po_2 was significantly higher in trial patients than in controls.

The mortality in RSI patients was 40.7% versus only 21.5% for matched controls (odds ratio, 2.51; 95% confidence interval, 1.33–4.72; $p < 0.01$). Table 6 displays mortality for RSI patients stratified by various factors related to oxygenation and ventilation as compared with their matched controls. Both the lowest and final $ETCO_2$ values were associated with increased mortality versus matched controls. In addition, there appeared to be an adverse effect of profound desaturations during RSI and hypoxia after intubation.

Table 3 Logistic Regression Analysis of Pre- and Postintubation Factors Using Mortality as the Outcome Measure[a]

RSI Factor	Adjusted OR (95% CI)
Preintubation	
Lowest Spo_2	0.31 (0.06–1.56)
Duration of desaturation	1.52 (0.69–3.35)
Postintubation	
Lowest Spo_2	1.39 (0.35–5.55)
Lowest $ETCO_2$	7.71[b] (1.03–58.03)
Final $ETCO_2$	9.94[b] (1.04–94.68)

OR, odds ratio; CI, confidence interval.

[a] Odds ratios are adjusted for age, sex, Head/Neck AIS, Chest AIS, Abdomen AIS, and mechanism of injury and are reported for a 10% change in Spo_2 (lowest pre- and post-Spo_2), a 10-mm Hg change in $ETCO_2$ (lowest and final $ETCO_2$), and per minute (duration of desaturation).

[b] $p < 0.05$.

DISCUSSION

The preliminary analysis of San Diego Paramedic RSI Trial data documented an adverse effect of paramedic RSI on outcome when compared with matched controls.[15] Three possibilities exist to explain these results. The increase in mortality may reflect some hidden bias introduced by the study design, although trial patients and controls appeared to have been identical with regard to each of the factors that we examined, including demographics, mechanisms of injury, vital signs, AIS scores for each body system, computed tomographic scan diagnoses, and invasive procedures.[15] These results may also represent a true-negative effect of intubation on head injury. To date, the evidence in support of early intubation is tangential at best, with a growing number of studies documenting an association between early intubation and mortality.[16,17] The final possibility is that factors associated with the RSI procedure as performed in our trial were

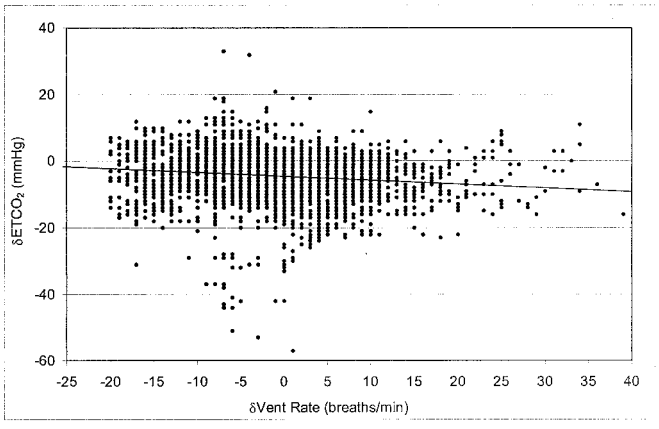

Fig. 2. *Linear regression analysis documenting a statistically significant association between the changes in $ETCO_2$ and ventilatory rate after a 90-second equilibration period (r = −0.13, p < 0.0001).*

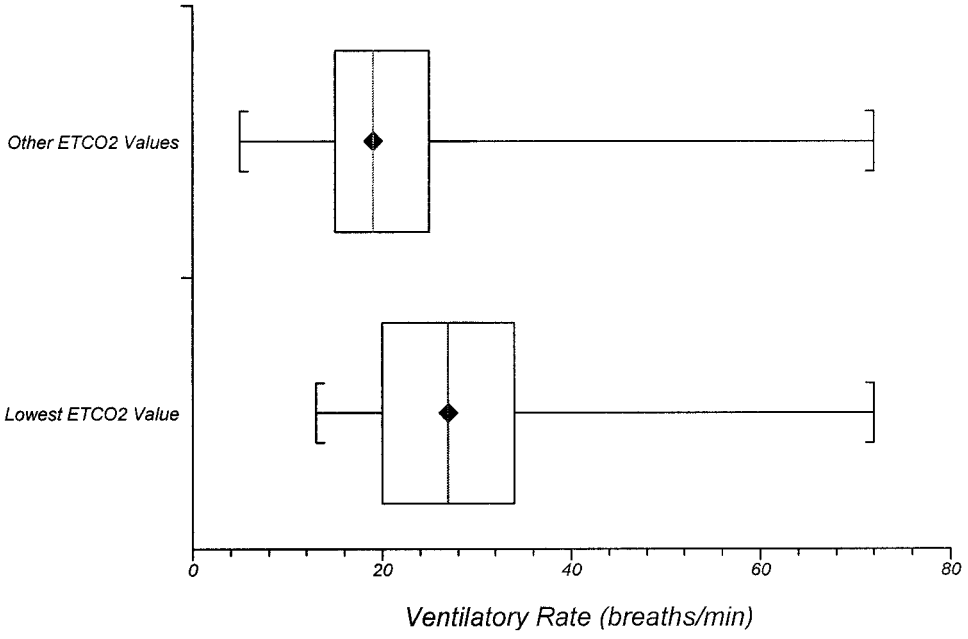

Fig. 3. *Box-and-whisker plot comparing ventilatory rate values associated with the lowest recorded $ETCO_2$ value versus all other $ETCO_2$ values. The* brackets *define the total range of values, the* edges *of each box define the lower and upper quartiles, and the* single lines *represent median values. A statistically significant difference between the two groups was observed ($p < 0.0001$).*

responsible for the increase in mortality, masking any potential benefit from the procedure. This is suggested by the high incidence of preintubation desaturation and postintubation hyperventilation observed in previous analyses.[15,18]

In this study, we explore the impact of these potentially avoidable factors on outcome. Our logistic regression model documents an independent association between both the lowest and final recorded $ETCO_2$ values and mortality; the lowest recorded Spo_2 value and duration of desaturation were not associated with an increase in mortality. The hypocapnia we observed appeared to be a result of excessively high ventilatory rates, as evidenced by both regression modeling and univariate analysis. The matched-controls analysis confirmed the adverse effect of hyperventilation on outcome. In addition, profound desaturations during RSI ($Spo_2 < 70\%$) and hypoxia after intubation ($Spo_2 < 90\%$) were both associated with higher mortality than in matched controls.

Both desaturations and hyperventilation represent errors in the performance of the RSI procedure and may explain some of the mortality increase we observed. It is interesting to note, however, that the absence of these factors did not lead to an improvement in survival over matched controls. Whether this reflects a true detrimental effect of early intubation on outcome or a form of selection bias in favor of controls should not detract from the most important findings of this analysis regarding the role of hyperventilation and deep desaturations on outcome in patients undergoing prehospital airway management. Future training and investigation involving prehospital intubation should address these issues to determine whether airway management with minimal complications leads to improved outcomes in patients with severe TBI.

Although hypoxia and hyperventilation are generally considered to be detrimental to the injured brain, little attention has been given to the impact of brief periods of hypoxia or hyperventilation during the resuscitation phase. Multiple studies have documented an association between early hypoxia and mortality in severely head-injured patients, although hypotension has consistently demonstrated a more profound effect.[1–4,19] None of these studies explored the impact of "iatrogenic" hypoxia in association with RSI. One group studied the effect of desaturations ($Spo_2 < 92\%$) in patients undergoing RSI caused by severe traumatic brain injury and found no difference in outcome, even after controlling for the potential contributions of other clinical variables.[20] Their threshold value may have been too high, as we observed an adverse effect of hypoxia on outcome only with extreme desaturations ($Spo_2 < 70\%$). Animal studies have documented an increase in neuronal death with brief (30 minutes) hypoxemia after experimental brain injury, although concurrent hypotension may have contributed to outcome in at least one of these.[21,22]

Stronger evidence exists for an immediate adverse effect of hyperventilation, although most studies have used surrogate endpoints, such as cerebral blood flow, tissue oxygenation, jugular venous oxygen saturation, and extracellular lactate and glutamate.[23–35] One notable exception is the multicenter trial performed by Muizelaar et al., which randomized severely head-injured patients to undergo moderate hyperventilation ($Pco_2 = 25$ mm Hg) or normal ventilation

Table 4 Age, Sex, Mechanism of Injury, Abbreviated Injury Scale Scores, and ISS for the RSI Cohort (n = 59) vs. Pooled Matched Controls (n = 177)

Parameter	RSI (%)	Controls (%)	*p* Value
Demographics			
Age (yr)	38.1	36.9	0.641
Male sex	81.3	81.3	>0.999
Mechanism of injury			
Motor vehicle crash	22.0	22.0	>0.999
Fall	32.2	32.2	>0.999
Assault	1.7	1.7	>0.999
Bike accident	8.5	8.5	>0.999
Motorcycle crash	3.4	3.4	>0.999
Pedestrian vs. automobile	11.9	11.9	>0.999
Gunshot wound	13.6	13.6	>0.999
Found down	3.4	3.4	>0.999
Other	3.4	3.4	>0.999
Abbreviated Injury Scale scores			
Head/Neck (mean)	3.92	3.92	>0.999
2	18.6	18.6	>0.999
3	13.6	13.6	>0.999
4	25.4	25.4	>0.999
5	42.4	42.4	>0.999
Face (mean)	0.46	0.60	0.309
0	76.3	68.9	0.283
1–2	18.6	24.9	0.328
3+	5.1	6.2	0.750
Chest (mean)	1.17	1.24	0.780
0	67.8	63.8	0.582
1–3	16.9	16.9	>0.999
4–6	15.3	19.2	0.496
Abdomen (mean)	0.53	0.67	0.475
0	83.1	76.8	0.315
1–3	11.9	17.5	0.307
4–6	5.1	5.6	0.869
Extremities (mean)	0.83	0.77	0.757
0	64.4	69.5	0.468
1–2	22.0	14.1	0.152
3+	13.6	16.4	0.605
Skin (mean)	0.80	1.03	0.016
0	35.6	18.1	0.005
1+	64.4	81.9	0.005
ISS (mean)	26.2	26.6	0.857

ISS, Injury Severity Score.

(P_{CO_2} = 35 mm Hg) for the first 5 days of hospitalization.[36] The increase in mortality observed in hyperventilated patients led to recommendations against the use of routine hyperventilation in traumatic brain injury. No previous investigators have explored the impact of prehospital hyperventilation on outcome.

Inadvertent hyperventilation is extremely common with manual ventilation, regardless of the personnel or setting.[37–41] We observed $ETCO_2$ values less than 25 mm Hg in 59% of patients for a mean duration of 390 seconds. This may have adverse effects on the injured brain through a variety of mechanisms. First, cerebral vasoconstriction with hypocapnia is well documented and can result in global ischemia through a decrease in cerebral blood flow as well as local ischemia, especially in critical areas of brain surrounding the primary injury.[23–35] Second, positive-pressure ventilation reverses the pattern of negative intrathoracic pressure associated with spontaneous respiration, potentially obstructing venous return and decreasing blood pressure and cardiac output; this occurs to a greater degree with increasing ventilatory rates.[42] Lastly, the increase in mean intrathoracic pressure that accompanies hyperventilation with positive-pressure ventilation can be transmitted in a retrograde fashion through the jugular venous system, raising intracranial pressure as a result. Recent data also suggest that injurious ventilation strategies lead to an increase in cytokine release, endothelial apoptosis, and mortality from both overinflation and from the absence of positive end-expiration pressure.[43–46] The specific characteristics of prehospital ventilation with regard to each of these factors has not been defined; however, it is possible that a lower $ETCO_2$ value is a surrogate marker for injurious ventilation.

Table 5 Arrival SBP, Arterial Blood Gas Values, and Serum Ethanol for RSI Patients (n = 59) vs. Matched Controls (n = 177)

	RSI	Controls	*p* Value
Arrival SBP			
Mean (mm Hg)	148.5	133.7	0.119
≤90 mm Hg (%)	8.5	9.0	>0.999
ABG data (mean)			
pH	7.34	7.34	0.897
P_{O_2} (mm Hg)	301	241	0.042
P_{CO_2} (mm Hg)	38.0	38.5	0.833
Base excess	−4.8	−4.4	0.678
Mean serum ethanol (mg/dL)	123	107	0.621

SPB, systolic blood pressure; ABG, arterial blood gas.

It is also notable that the increase in mortality observed in trial patients was consistent with our previous analyses, despite complete original matching of historical controls.[15] Trial patients and controls were identical with regard to all matching parameters as well as initial SBP and serum ethanol. There was a predicted increase in arrival P_{O_2} for trial patients; however, mean P_{O_2} in controls was supratherapeutic at 241 mm Hg. In addition, there were no observed differences with regard to the above parameters between RSI patients and their matched controls when trial patients were stratified into those with and without recorded $ETCO_2$ values below 20 mm Hg. There were also no apparent differences between the two groups of trial patients that could account for the lower $ETCO_2$ values.

These data must be viewed in the context of study limitations. This subset of patients represents a relatively small percentage of the total group of trial patients, with limited power to find associations between the various factors and outcome. Nevertheless, we were able to identify hypocapnia caused by hyperventilation as a potential contributor. In addition, patients were not randomized to undergo hyperventilation versus normal ventilation, and hyperventilation may have been a surrogate marker for more severe injuries that

Table 6 Odds Ratio Analysis of Pre- and Postintubation Factors Comparing RSI Trial Patients to Their Matched Controls[a]

RSI Factor	No.	Mortality for RSI Patients (%)	Mortality of Matched Controls (%)	Odds Ratio (95% CI)
During RSI				
Lowest Spo_2 (%)				
≥90%	16	37.5	14.6	3.51 (0.97–12.78)
70–89%	17	35.3	29.4	1.31 (0.41–4.19)
<70%	16	43.7	16.7	3.89[b] (1.12–13.52)
Duration of desaturation				
0 s	15	40.0	15.6	3.62 (0.98–13.42)
1–120 s	15	26.7	15.6	1.97 (0.49–8.00)
>120 s	18	50.0	27.8	2.60 (0.87–7.80)
Postintubation				
Lowest Spo_2				
>95%	19	21.1	12.3	1.90 (0.49–7.40)
90–95%	17	47.1	21.6	3.23[b] (1.01–10.34)
<90%	16	56.3	25.0	3.86[b] (1.18–12.61)
Lowest $ETCO_2$ value				
>27 mm Hg	18	22.2	16.7	1.43 (0.38–5.36)
20–27 mm Hg	19	47.4	21.1	3.38[b] (1.12–10.17)
<20 mm Hg	17	47.1	19.6	3.64[b] (1.12–11.82)
Final $ETCO_2$ value				
>32 mm Hg	17	29.4	17.6	1.94 (0.55–6.91)
24–32 mm Hg	18	44.4	22.2	2.80 (0.90–8.66)
<24 mm Hg	19	42.1	15.8	3.88[b] (1.22–12.32)

CI, confidence interval.
[a] Trial patients were stratified for each of the factors explored in the logistic regression analysis.
[b] $p < 0.05$.

were not detected by our analysis. Finally, data were not available regarding the prehospital oxygenation and ventilation of controls, although none was intubated in the field, avoiding the potentially detrimental effects of positive-pressure ventilation and hyperventilation.

CONCLUSION

In this study, we explored the potential impact of hypoxia and hypocapnia on outcome in severely head-injured patients undergoing paramedic RSI. A relationship between hypocapnia and an increase in mortality was observed; in addition, this hypocapnia appeared to be a result of excessively high ventilatory rates despite protocols designed to target a ventilatory rate of 12 breaths/min. Matched controls analysis revealed worse outcomes in RSI patients versus matched controls, especially in the presence of any degree of hypocapnia and with deep desaturations during laryngoscopy.

ACKNOWLEDGMENTS

We thank the San Diego County Base Hospital and Trauma Departments, American Medical Response, San Diego Medical Services Enterprise, Mercy Air, county flight nurses, the RSI Educational Task Force and trainers, paramedic provider agency coordinators, Palomar and Southwestern Colleges, the County of San Diego Division of EMS biostatistical team, the California EMS Authority, and especially the paramedics throughout San Diego County whose enthusiastic support made the study possible. We particularly thank David Bailey, RN, Ginger Ochs, RN, Gina Anderson, RN, Kelly Forman, RN, and Mark Angeloni, RN, for their training contributions.

REFERENCES

1. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma.* 1993;34:216–222.
2. Pigula FA, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. *J Pediatr Surg.* 1993;28:310–316.
3. Kokoska ER, Smith GS, Pittman T, Weber TR. Early hypotension worsens neurological outcome in pediatric patients with moderately severe head trauma. *J Pediatr Surg.* 1998;33:333–338.
4. Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma.* 1996;40:764–767.
5. Winchell RJ, Hoyt DB. Endotracheal intubation in the field improves survival in patients with severe head injury: Trauma Research and Education Foundation of San Diego. *Arch Surg.* 1997;132:592–597.
6. Falcone RE, Herron H, Dean B, Werman H. Emergency scene endotracheal intubation before and after the introduction of a rapid sequence induction protocol. *Air Med J.* 1996;15:163–167.
7. Davis DP, Ochs M, Hoyt DB, Bailey D, Marshall LK, Rosen P. Paramedic-administered neuromuscular blockade improves prehospital intubation success in severe head-injured patients. *J Trauma.* 2003;55:713–719.
8. Smith JP, Bodai BI. The urban paramedic's scope of practice. *JAMA.* 1985;253:544–548.
9. McDonald CC, Bailey B. Out-of-hospital use of neuromuscular-blocking agents in the United States. *Prehosp Emerg Care.* 1998; 2:29–32.
10. Wayne MA, Friedland E. Prehospital use of succinylcholine: a 20-year review. *Prehosp Emerg Care.* 1999;3:107–109.
11. Vilke GM, Hoyt DB, Epperson M, Fortlage D, Hutton KC, Rosen P. Intubation techniques in the helicopter. *J Emerg Med.* 1994;12:217–224.

12. Sing RF, Reilly PM, Rotondo MF, Lynch MJ, McCans JP, Schwab CW. Out-of-hospital rapid-sequence induction for intubation of the pediatric patient. *Acad Emerg Med.* 1996;3:41–45.
13. Pace SA, Fuller FP. Out-of-hospital succinylcholine-assisted endotracheal intubation by paramedics. *Ann Emerg Med.* 2000; 35:568–572.
14. Ochs M, Davis D, Hoyt D, Bailey D, Marshall L, Rosen P. Paramedic-performed rapid sequence intubation of patients with severe head injuries. *Ann Emerg Med.* 2002;40:159–167.
15. Davis DP, Hoyt DB, Ochs M, et al. The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. *J Trauma.* 2003;54:444–453.
16. Eckstein M, Chan L, Schneir A, Palmer R. Effect of prehospital advanced life support on outcomes of major trauma patients. *J Trauma.* 2000;48:643–648.
17. Murray JA, Demetriades D, Berne TV, et al. Prehospital intubation in patients with severe head injury. *J Trauma.* 2000;49:1065–1070.
18. Dunford JV, Davis DP, Ochs M, Doney M, Hoyt DB. The incidence of transient hypoxia and heart rate reactivity during paramedic rapid sequence intubation. *Ann Emerg Med.* 2003;42:721–728.
19. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl.* 1993;59:121–125.
20. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Arch Surg.* 2001;136:1118–1123.
21. Bramlett HM, Green EJ, Dietrich WD. Exacerbation of cortical and hippocampal CA1 damage due to posttraumatic hypoxia following moderate fluid-percussion brain injury in rats. *J Neurosurg.* 1999; 91:653–659.
22. Clark RS, Kochanek PM, Dixon CE, et al. Early neuropathologic effects of mild or moderate hypoxemia after controlled cortical impact injury in rats. *J Neurotrauma.* 1997;14:179–189.
23. Manley GT, Hemphill JC, Morabito D, et al. Cerebral oxygenation during hemorrhagic shock: perils of hyperventilation and the therapeutic potential of hypoventilation. *J Trauma.* 2000;48:1025–1033.
24. Feracaakovaa A, Vanickay I, Marasala M, Marasala J. Effect of prolonged hyperventilation on ischemic injury of neurons after global brain ischemia in the dog. *J Hirnforschung.* 1995;36:297–304.
25. Fortune JB, Feustel PJ, Graca L, Hasselbarth J, Kuehler DH. Effect of hyperventilation, mannitol, and ventriculostomy drainage on cerebral blood flow after head injury. *J Trauma.* 1995;39:1091–1099.
26. Skippen P, Seear M, Poskitt K, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. *Crit Care Med.* 1997;25:1402–1409.
27. Yundt KD, Diringer MN. The use of hyperventilation and its impact on cerebral ischemia in the treatment of traumatic brain injury. *Crit Care Clin.* 1997;13:163–184.
28. Moore C, Flood C. Hyperventilation in head injury does it do more harm than good? *Axone.* 1993;15:30–33.
29. Newell DW, Weber JP, Watson R, Aaslid R, Winn HR. Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after severe head injury. *Neurosurgery.* 1996;39:35–44.
30. Schneider GH, Sarrafzadeh AS, Kiening KL, Bardt TF, Unterberg AW, Lanksch WR. Influence of hyperventilation on brain tissue-PO2, PCO2, and pH in patients with intracranial hypertension. *Acta Neurochir Suppl.* 1998;71:62–65.
31. Weckesser M, Posse S, Olthoff U, Kemna L, Dager S, Muller-Gartner HW. Functional imaging of the visual cortex with bold-contrast MRI: hyperventilation decreases signal response. *Magn Reson Med.* 1999;41:213–216.
32. Diringer MN, Yundt K, Videen TO, et al. No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury. *J Neurosurg.* 2000;92:7–13.
33. Diringer MN, Videen TO, Yundt K, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. *J Neurosurg.* 2002;96:103–108.
34. Ausina A, Baaguena M, Nadal M, et al. Cerebral hemodynamic changes during sustained hypocapnia in severe head injury: can hyperventilation cause cerebral ischemia? *Acta Neurochir Suppl.* 1998;71:1–4.
35. Dings J, Meixensberger J, Amschler J, Roosen K. Continuous monitoring of brain tissue PO2: a new tool to minimize the risk of ischemia caused by hyperventilation therapy. *Zentralbl Neurochirur.* 1996;57:177–183.
36. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg.* 1991;75:731–739.
37. Thomas SH, Orf J, Wedel SK, Conn AK. Hyperventilation in traumatic brain injury patients: inconsistency between consensus guidelines. *J Trauma.* 2002;52:47–53.
38. Braman SS, Dunn SM, Amieo CA. Complications of intrahospital transport in critically ill patients. *Ann Intern Med.* 1987;107:469–473.
39. Gervais HW, Eberle B, Konietzke D, Hennes HJ, Dick W. Comparison of blood gases of ventilated patients during transport. *Crit Care Med.* 1987;15:761–763.
40. Hurst JM, Davis K, Branson R, Johannigman JA. Comparison of blood gases during transport using two methods of ventilatory support. *J Trauma.* 1989;29:1637–1640.
41. Tobias JD, Lynch A, Garrett J. Alterations of end-tidal carbon-dioxide during the intrahospital transport of children. *Pediatr Emerg Care.* 1996;12:249–251.
42. Pepe PE, Raedler C, Lurie KG, Wigginton JG. Emergency ventilatory management in severe hemorrhagic states: elemental or detrimental? In: Brasel K, ed. American Association for the Surgery of Trauma. Orlando, FL, 2002:80.
43. Chiumello DE, Pristine G, Slutsky AS. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999; 160:109–116.
44. Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA.* 2003;289:2104–2112.
45. Johannigman JA, Miller SL, Davis BR, Davis K Jr, Campbell RS, Branson RD. Influence of low tidal volumes on gas exchange in acute respiratory distress syndrome and the role of recruitment maneuvers. *J Trauma.* 2003;54:320–325.
46. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301–1308.

DISCUSSION

Dr. Norman E. McSwain (New Orleans, Louisiana): I am pleased to substitute for Dr. Johannigman, since he is in Iraq. The authors are to be congratulated for this study.

First, they looked at the results of the RSI intubation study that they had conducted previously and found a significant difference. However, went further by asking the question, why.

It would be nice to know the exact comparison of the groups in the previous study and this group. They found that the differences are oxygen saturation of less than 70% during RSI, oxygen saturation after intubation greater than or less than 90% $ETCO_2$ less than 20 after intubation, and $ETCO_2$ less than 24 as a final factor.

This seems to be very important as we direct our own Emergency Medical Services (EMS) and return to our communities and institute changes to improve patient care. However, before we rush into making changes, there is more information that we need.

First, when we return to our EMS systems that may not be equipped with digital capnography, and most are not in the United States, what are we going to tell our EMS personnel to do? Don't hyperventilate the patient?

Unfortunately, the authors did not define this in terms Emergency Medical Technicians have the ability to control. The authors did not tell us exactly what ventilatory rates achieved the various $ETCO_2$ values that they felt were bad.

If you cannot supply those data today, I would suggest you include it in your final article. Otherwise, it's worthless information for medical directors in the United States.

Second, it concerns me that this was not a randomized study. If we're going to go home and make changes, do we know that these are actually compatible groups?

It seems to me that the patients were intubated on the basis of a GCS score of less than 8. However, in the historical control, we don't know what GCS score levels the controls had in the matching groups, and we don't have a GCS score comparison in those groups.

The authors pointed out in other studies that in-hospital $ETCO_2$ values kept at a lower level produced a bad outcome. Unfortunately, they did not tell us any of the in-hospital CO_2 values or any of the other variables within the hospital, which might make this an "apples and oranges" comparison. Would you please address this issue?

Fourth, this study discusses patients with RSI intubations, but patients that were intubated without RSI were not included. Is there a difference?

Fifth, if these were two matched groups of patients, why was there a difference in blood pressure in the RSI group, which was much higher, although not statistically significant, than patients without head injuries? Sixth, I would suggest that you change the title of your article and the selection of words throughout from "hyperventilation" to "decreased $ETCO_2$."

Hyperventilation to the EMS community is a rate. You do not define this in rates. Therefore, it may be misleading to the medical directors.

Finally, now that you have found a worse outcome with RSI, do you still allow its use in your own system? If so, how can you justify its use? We wish Dr. Johannigman a good experience in Iraq and a fast, safe return, and I appreciate the opportunity to discuss this article.

Dr. Jeffrey P. Salomone (Atlanta, Georgia): I applaud the efforts to investigate the reasons why patients treated with RSI by paramedics had a worse outcome. My question focuses on what measures were taken to limit hypoxia and hypercarbia during the intubation attempts. Thank you for pursuing this investigation on a very important issue in prehospital care.

Dr. Michael L. Hawkins (Atlanta, Georgia): First, you did not discuss at all the transport times. In a closed, fairly small system in San Diego, it may be quite different from what I deal with in a semirural, fairly large state.

Second, you state that the bag-valve-mask is equally effective as intubation. How about patients with significant facial trauma or, on a personal level, patients with facial hair. It might be a bit of a problem to obtain a good seal. Finally, it seems to me that your study really didn't show that RSI was dangerous but that the management after RSI was dangerous, and that alludes to several of the points Dr. McSwain already raised.

Dr. Eileen M. Bulger (Seattle, Washington): I have concerns similar to those of Dr. McSwain about the matching of the control groups and wonder whether you have data on the GCS score or the prehospital GCS scores of the controls. The other question I have is, do you have data on the intubation rates of the controls in the emergency department? If they were intubated in the emergency department, do you have any data on hypoxia during intubation in that setting? Thank you.

Dr. James Tyburski (Detroit, Michigan): We've had a lot of interest in $ETCO_2$ relationships to the arterial CO_2. In our data of well over 500 patients undergoing surgery, we found that the difference was more important. Are there any data here comparing the difference between the $ETCO_2$ and the $PaCO_2$ values in the measurements? Thank you.

Dr. Richard P. Dutton (Baltimore, Maryland): I wanted to ask about the matching of controls, whether the authors made any effort to identify variables that might not show up in an AIS match but might influence the paramedic to intubate a patient in the field, such as combativeness, active aspiration, or acute pain.

Dr. Graham (Baltimore, Maryland): I just wanted to congratulate the authors on an article that supports our findings that we presented at the Western Association for the Surgery of Trauma meeting last year, but I do have one question. A recent article from Hellmann College in a randomized prospective trial using $ETCO_2$ monitoring of prehospital patients had found that $ETCO_2$ monitoring actually decreased hypoventilation and increased normal ventilation. My question is, why did your findings not also support these randomized prospective trial findings?

Dr. Jean-Francois Pittet (San Francisco, California): An important issue is allowing the paramedics to use paralytic agents for endotracheal intubation outside the hospital. I would like to know in how many cases there has been a failed

intubation or a repeated attempt to intubate those patients. I think it's a critical issue here. Thank you.

Dr. Daniel Davis (closing): Thank you very much, Dr. McSwain, especially because you had to fill in at the last minute and really only received the article last week. There are a lot of questions here, all of which are excellent, and I'm going to try to address them because I think these are important, especially for those who have some control over their EMS system.

I'm going to start with Dr. McSwain's questions. The respiratory rate data are actually going to be presented in a separate article but, given that the parameters given to the medics were that they should keep the respiratory rate around 12 breaths/min, it is significant to note that the mean maximum respiratory rate was approximately 50 breaths/min in these patients in whom $ETCO_2$ monitoring was performed.

We were able to show that the patients who had lower oxygen saturation values after intubation had higher respiratory rates, and so there may have been some attempt by the medics to improve oxygenation by increasing respiratory rate; however, in a regression analysis, there was no relationship between the oxygen saturation and the respiratory rate. So I think that's an important issue that needs to be addressed, and I'll talk more about that.

I think the biggest limitation of this study is that it's not randomized, and several people have brought that up. Also, there may have been inherent biases in the control group or in favor of the control group.

We have looked at multiple aspects of the matching, including the actual computed tomographic scan diagnoses, and that's presented in a separate article, and have not been able to show any particular difference that could account for the differences in outcomes. So thus far, we have not observed that there is some bias or some inherent difference between the groups; however, one question was regarding the GCS score, which was not routinely calculated in the field before this study, but was instead entered in by a Mobile Intensive Care Nurse based on data given to the medics, which is notoriously inaccurate, and so that may be a hidden bias that we can't account for and we'll never know, and only a prospective randomized trial would be able to answer this question.

With regard to the absence of hospital data in this particular analysis, our previous analyses have demonstrated that there is a correlation between arrival P_{CO_2} and outcome, and so hyperventilation or hypocapnia would probably be the preferred term. It does appear to have an effect no matter how we look at it, whether it's through $ETCO_2$ monitoring or arrival blood gas.

An important question with regard to patients intubated with RSI and that will be published I believe this month or next month in the *Journal of Trauma* concerned a comparison between the first year of the trial and the previous year. We actually noted that the percentage of patients intubated without RSI medications went up during the trial, and so our concern was that patients who could have been intubated without medication would be given medication as part of the trial, and the opposite seems to be true. If anything, that should have favored the RSI group, leaving more neurologically intact patients as part of the trial cohort.

The blood pressure in RSI group was not statistically significantly higher, although it was higher, and whether that reflects the low amount of midazolam used as part of the trial and some sort of adverse reaction by the patient is not certain. That has been one of the criticisms, and that was based on concern for hypotension caused by midazolam, which was shown in a previous study using heir medical data.

I think one of the most important questions has to do with the terminology and the issue of "hyperventilation" as a term versus "hypocapnia" and the possibility that these are really just surrogates for some other injury pattern in these patients that led the medics to ventilate them faster or with deeper tidal volumes. There is increasing data suggesting that ventilation strategies may play an important role, especially early in the course of a resuscitation, and that includes the release of cytokines and apoptosis of endothelial cells. Thus, I think this is an area that needs further research.

As far as what you would tell your paramedic crews at this time, I think that $ETCO_2$ monitoring has to become part of the culture of prehospital medicine because there is no other way to avoid it. Only further research is going to determine whether this will erase that adverse effect of prehospital intubation and paramedic RSI. Thank you.