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Impact of pre-hospital oxygenation and ventilation status on outcome in patients with isolated severe traumatic brain injury

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ABSTRACT

Introduction. Hypoxia is one of the secondary insults and it worsens the outcome in patients with severe traumatic brain injury (TBI). On the other hand, there is some controversy about the impact of hyperoxia on the outcome in these patients. The aim of the study was to determine the impact of pre-hospital hypoxia, hyperoxia and pre-hospital ventilation status on outcome after isolated TBI.

Methods. We retrospectively reviewed charts from patients with isolated severe TBI who underwent pre-hospital endotracheal intubation. The population was sorted into groups based on PaO_2 (hypoxic, PaO_2 <100 mmHg; normoxic, PaO_2 100-200 mmHg; hyperoxic, PaO_2 > 200 mmHg) and initial Glasgow Coma Scale (GCS) level (3-5 and ≥ 6). Ventilation status was defined as: hypocarbic ($PaCO_2$ < 35 mmHg), normocarbic ($PaCO_2$ 35-45 mmHg) and hypercarbic ($PaCO_2$ > 45 mmHg).

Results. Oxygenation status had no significant impact on 24- and 48-hour survival, on the length of hospital stay or on neurological outcome (measured by the Glasgow Outcome Scale (GOS), Glasgow Pittsburgh Cerebral Performance Categories Scale (CPC), and GCS score at discharge) when all six groups were compared together. We were unable to prove a deleterious effect of hypoxia or hyperoxia compared to normoxia on rate of survival to hospital discharge (STHD) (0.38 (0.52) vs 0.50 (0.51) vs 0.65 (0.49), where 0 - no and 1 - yes; f = 1.246, p = 0.298). Ventilation status also failed to significantly affect survival and functional outcome in patients with isolated severe TBI.

Conclusion. Pre-hospital oxygenation and ventilation status have no significant impact on outcome in patients with isolated severe TBI.

Key words: hypoxia, pre-hospital, intubation, hyperventilation, traumatic brain injury

Introduction

Therapeutic strategies in patients with severe traumatic brain injury (TBI) are focused on prevention of a chain of events called secondary brain injury which can worsen brain injury once it has occurred. Hypoxia is one of the secondary insults and its effect on outcome is well established. (1) It was also recognized by the Brain Trauma Foundation which published 'The Guidelines for the Management of Severe Traumatic Brain Injury' in 2007 and recommended that hypoxia (PaO_2 < 60 mmHg) in patients with severe TBI should be avoided. (2)

On the other hand, there is some controversy about hyperoxia. Some studies have found a beneficial effect with improved physiological parameters, (3,4) while others have reported worsened functional outcome. (5,6)

Endotracheal intubation (ETI) using a rapid sequence intubation (RSI) protocol was introduced to pre-hospital Emergency Medical Services (EMS) to avoid hypoxia and to secure the airway, thus preventing aspiration in patients with TBI. Aggressive early airway management increases the success of pre-hospital ETI, but surprisingly also increases the mortality rate. (7,8) The suggested causes for this finding are hyperventilation (9) and positive pressure ventilation; (10) both

Table 1. Baseline Characteristics.

	Hypoxia		Normoxia		Hyperoxia	
	GCS 3-5	GCS ≥ 6	GCS 3-5	GCS ≥ 6	GCS 3-5	GCS ≥ 6
Sample size	**4**	**4**	**12**	**11**	**9**	**9**
Male sex, n (%)	4 (100)	4 (100)	11 (92)	8 (73)	6 (67)	7 (78)
Age (Years)	43 (11)	59 (15)	39 (19)	45 (23)	42 (21)	56 (16)
Systolic BP (mmHg)	174 (32)*	120 (33)	129 (30)	138 (35)	130 (33)	150 (26)
Respiratory Rate (min^{-1})	15 (11)	12 (5)	11 (5)	16 (7)	9 (6)	13 (6)
Type of Trauma (Blunt-1/Sharp-2)	1.3 (0.5)	1.5 (0.6)	1.3 (0.5)	1.2 (0.4)	1.1 (0.3)	1.2 (0.4)

Numbers are mean (SD). There was a statistically significant interaction between pO_2 status and initial Glasgow Coma Scale (GCS) score for systolic blood pressure (BP).
* $p<0.05$ denotes statistically significant difference between GCS groups.

have detrimental effects on hemodynamic parameters resulting in ischemia and worsened functional outcome in patients with TBI.

The purpose of this single center retrospective study was to determine the impact of pre-hospital oxygenation and pre-hospital ventilation status on mortality rate and functional outcome at discharge in patients with isolated TBI in the emergency physician led pre-hospital EMS.

Materials and methods

Statement of human rights

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia, deciding that the study can be conducted without informed consent from participants.

EMS system in Maribor, Slovenia

This study was conducted in Maribor, Slovenia. The Center for Emergency Medicine in Maribor hosts the Maribor EMS system, which also includes two emergency physician-led advanced life support (ALS) teams. The patients with isolated TBI were treated according to current guidelines and were transported to the Emergency Department (ED) of the University Clinical Center of Maribor.

Study design

We retrospectively reviewed charts of patients with isolated TBI who underwent ETI using the RSI method between January 2000 and December 2012. We would like to emphasize that our emergency physicians working in the EMS are well trained in advanced life support skills and have been using the RSI protocol to secure the airway since the beginning of 2000. Since then, all patients with isolated TBI and Glasgow Coma Scale (GCS) less than 8 at the scene have undergone pre-hospital ETI using the RSI method. Endotracheal placement of the tube is confirmed by measuring the partial pressure of end tidal carbon dioxide ($petCO_2$) *in vivo.* These data were not well documented in charts, so they were not included in the study. Patients with isolated TBI were mechanically ventilated after ETI. Parameters (minute volume, respiratory frequency) on transport ventilators were selected by emergency physicians. All patients enrolled in the study were intubated during the first attempt. There were no misplaced tubes. The patients were transported to the ED on transport ventilators with an inspired oxygen concentration of 100%.

Patients with isolated TBI and initial GCS level less than 8 were defined as severe isolated TBI patients. Patients with isolated TBI and initial GCS level more than 9, whose GCS level deteriorate during transport to less than 8 and were intubated during transport, were also defined as severe isolated TBI patients. Six patients from the second group were enrolled in the study.

The arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$) values were obtained from initial arterial blood gas analysis immediately upon arrival in the ED. The cutoff values of PaO_2 were <100 mmHg (hypoxic group), 100-200 mmHg (normoxic group) and $>$ 200 mmHg (hyperoxic group). The population was sorted into six groups based on PaO_2 (hypoxic, normoxic, hyperoxic) and GCS level (3-5 and ≥ 6). The population, according to the ventilation status, was sorted based on initial $PaCO_2$ into three groups: hypocarbic/hyperventilated ($PaCO_2 < 35$ mmHg), normocarbic/normoventilated ($PaCO_2$ 35 - 45 mmHg) and hypercarbic/hypoventilated ($PaCO_2 > 45$ mmHg). Mortality rate was defined by in-hospital death of any cause. Functional outcome was measured using Glasgow Outcome Scale (GOS), Glasgow Pittsburgh Cerebral Performance Categories Scale (CPC) and GCS level at the discharge from hospital.

Statistical analysis

SigmaPlot 11.0 (Systat Software, Point Richmond, CA) was used for the statistical analysis. Two-way ANOVA was used to test for the effects of oxygenation status and GCS and their interaction. One-way ANOVA was used to compare the effects of ventilation status

Table 2. Survival and Functional Outcomes According to Oxygenation Status.

	Hypoxia		Normoxia		Hyperoxia	
	GCS 3-5	GCS ≥ 6	GCS 3-5	GCS ≥ 6	GCS 3-5	GCS ≥ 6
Sample size(n)	4	4	12	11	9	9
24h Survival (Yes-1/No-2)	1.0 (0.0)	1.0 (0.0)	1.1 (0.3)	1.0 (0.0)	1.2 (0.4)	1.1 (0.0)
48h Survival (Yes-1/No-2)	1.3 (0.5)	1.0 (0.0)	1.3 (0.5)	1.0 (1.0)	1.2 (0.4)	1.2 (0.4)
CPC at Discharge	3.7 (2.3)(3)	4.0 (2.0)	3.4 (2.0)	1.8 (1.0)	3.6 (1.8)	2.8 (2.0)
GOS	2.0 (2.0)	2.0 (2.0)	2.4 (1.8)	3.7 (1.3)	2.4 (1.8)	3.0 (2.0)
GCS at Discharge	15(1)	15(1)	14.8 (0.5)(5)	14.2 (1.5)(10)	12.8 (4.5)(4)	14.8 (0.4)(5)
Length of Stay (Days)	6.8 (6.2)	29.3 (36.7)	13.7 (22.0)	24.8 (30.2)	24.9 (44.5)	14.1 (14.2)

Numbers are mean (SD).
CPC, Glasgow Pittsburgh Cerebral Performance category; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale.
Numbers in brackets denote number of available data if it differs from the sample size. There were no overall statistically significant differences among groups.

Table 3. Survival and Functional Outcomes According to Ventilation Status.

	Hypocarbia	Normocarbia	Hypercarbia
Sample size (n)	14	25	10
24h Survival (Yes-1/No-2)	1.1 (0.4)	1.1 (0.2)	1.1 (0.3)
48h Survival (Yes-1/No-2)	1.2 (0.4)	1.2 (0.4)	1.1 (0.3)
Survival to Hospital Discharge (Yes-1/No-2)	1.5 (0.5)	1.4 (0.5)	1.5 (0.5)
CPC at Discharge	3.0 (1.9)(12)	3.0 (1.9)(24)	3.1 (2.0)
GOS	2.6 (1.8)	2.8 (1.8)	2.9 (2.0)
GCS at Discharge	13.6 (3.4)(7)	14.4 (1.3)(14)	14.8 (0.5)(5)
Length of Stay (Days)	20.5 (35.8)	18.8 (26.2)	17.3 (24.0)

Numbers are mean (SD).
CPC, Glasgow Pittsburgh Cerebral Performance Category; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale.
Numbers in brackets denote number of available data if it differs from the sample size. There were no overall statistically significant differences among groups.

on outcome. The data were presented as means (SD). A two-tailed value of $p<0.05$ was considered significant.

Results

There were no significant differences between groups at baseline except for systolic blood pressure, which was significantly higher in the hypoxic GCS 3-5 group (table 1).

Oxygenation status (i.e. hypoxia, normoxia and hyperoxia) had no significant impact on 24- and 48-hour survival or on the length of hospital stay. We were unable to prove a deleterious effect of hypoxia or hyperoxia compared to normoxia on rate of survival to hospital discharge (STHD) (0.38 (0.52) vs 0.50 (0.51) vs 0.65 (0.49), where 0 - no and 1 - yes; $f = 1.246$, $p = 0.298$). There was also no effect on neurological outcome (measured by the CPC, GOS, and GCS score at discharge) when all six groups were compared together (table 2).

Ventilation status (i.e. hypocarbic/hyperventilated,normocarbic/normoventilated, and hypercarbic/hypoventilated groups) also failed to significantly affect survival and functional outcome (table 3).

Discussion

The detrimental effect of hypoxia has been well studied (1) and is frequently found in patients after TBI at the accident scene. (11) Episodes of hypoxia are a common secondary insult in the pre-hospital setting and intensive care units (ICU) and increase the mortality rate and the degree of disability at discharge. (12,13) The duration of the hypoxic episode also plays a role. Longer hypoxic episodes increase the mortality rate. (12,14) Taking this into consideration, it is recommended by guidelines to avoid hypoxia ($PaO_2 < 60$ mmHg) in patients with severe TBI. (2)

There is some controversy about the impact of hyperoxia on brain tissue in patients with TBI. Some studies showed improved cerebral metabolism parameters such as increase in brain tissue PO_2, reduced lactate (3) and glutamate levels and reduced lactate/pyruvate ratio. (4) Increased brain PO_2 should improve the cerebral metabolism through improved mitochondrial function. This hypothesis is supported by animal studies that show increased levels of adenosine triphosphate (ATP) in hyperoxic rats following lateral fluid-percussion injury. (15)

On the other hand, hyperoxia did not improve the cerebral metabolic rate for oxygen measured with positron emission tomography (PET). (16) Hyperoxia also causes vasoconstriction and thus reduced intracranial pressure (ICP) (4) and cerebral blood flow. Presum-

ably the increase in oxygen carrying capacity by hyperoxia outweighed the reduction in blood flow. (17) Although they found some beneficial effects of hyperoxia in brain micro dialysate they did not observe improved functional neurological outcome in hyperoxemic patients with TBI. Moreover, studies have shown that hyperoxia has a detrimental effect on functional neurological outcome in patients with TBI. (5,6)

At first glance, our findings from the study do not support the thesis that pre-hospital hypoxia and hyperoxia are detrimental to the injured brain. At this point we would like to emphasize that interpretation of our data should be put into perspective of the small sample size. When we hypothetically doubled the number of patients in the compared groups with the same patients' characteristics used in the original comparison there was a clear statistically significant effect of the interaction between oxygenation status and GCS score on the rate of survival to hospital discharge. There was also a clear beneficial effect of normoxemia compared to hypo- and hyperoxemia on STHD in the group of patients with an initial GCS $\geq$ 6.

A considerable percentage (16 %) of hypoxic patients in our study raises some questions. Five patients from the hypoxic group were hypoventilated, while the others were normoventilated. We believe that TBI evokes pulmonary complications causing hypoxia in normoventilated patients. (18,19) The possible beneficial effect of early out-of-hospital intubation to secure the airway and to prevent hypoxia and aspiration has been questioned. Many studies have shown that a pre-hospital ETI in patients with TBI is associated with increased mortality. In most of these studies pre-hospital intubation was performed by non-physician pre-hospital personnel with limited ETI training and clinical skills and who did not have full access to the drugs used during RSI protocol. (7,8,20,21) It is likely that the patients who can be intubated in the field without RSI medications have a more devastating neurologic injury compared to those who need RSI medications and as a consequence less favorourable outcome. Increased mortality was observed even when patients with TBI underwent paramedic RSI, due to severe hypoxia and hyperventilation during paramedic RSI. (22) Some of the studies observed improved mortality rate when the ETI was done in the ED (8,20) or performed by air ambulance personnel (using neuromuscular blocking agents). (23,24) There was no difference observed in patient outcome after pre-hospital ETI by aeromedical crew using RSI protocol compared to undergoing ETI in a trauma resuscitation suite. (25)

It is reasonable to assume that the procedure (ETI) itself and possible complications (22,26,27) during ETI are connected with patient outcome.

The possible detrimental impact of pre-hospital intubation is associated with the risk of hyperventilation and positive pressure ventilation. Hyperventilation (9) and hypoventilation (28,29) in intubated patients with TBI increase the mortality rate. Only targeted pre-hospital ventilation is associated with lower mortality rate. (30)

Hypocapnia due to hyperventilation causes cerebral vasoconstriction of precapillary resistance vessels and can result in global ischemia through a decrease in cerebral blood flow and diminished brain oxygenation. Positive pressure ventilation increases intrathoracic pressure, which reduces the venous return and decreases blood pressure and cardiac output. (10,22,28) Increased intrathoracic pressure can be retrogradely transmitted through the jugular venous system raising intracranial pressure as a result. (31) However, hyperventilation reduces ICP through vasoconstriction (17) and is recommended as a treatment in patients with acute brainstem herniation. (32) The proposed mechanism of the detrimental effect of hypoventilated/hypercarbic patients is suboptimal vasoreactivity to carbon dioxide (CO_2), with preserved CO_2 vasoreactivity to hyperventilation, but buffered vasodilatation to hypoventilation. This would cause relative ischemia precipitating secondary brain injury in both hypocarbic and hypercarbic patients. In addition, an increase in cerebral blood flow in the hypoventilated group could raise ICP above the critical threshold and increase mortality. (29)

Findings from our study do not support the results from previously mentioned studies. Ventilation status failed to significantly affect survival and functional outcome in patients after isolated TBI. Our study showed that nearly half (49 %) of the patients with isolated TBI were not optimally ventilated. We assume that this is due to over- or under estimation of patient's ideal body weight and high frequency ventilation and consequently led to inappropriate pre-hospital ventilation. The use of continuous monitoring of $petCO_2$ could be helpful in preventing inadvertent severe hyperventilation. (33) In addition, blood gas measurements of pO_2 and pCO_2, from portable devices, are acceptable surrogates to standard clinical laboratory blood gas measurements in guiding protocol-directed ventilator management. (34)

Our study has several limitations. Firstly, this is a non-randomized retrospective study. The nature of the study by itself could include some biases. Secondly, the sample size is small. Thirdly, arrival arterial blood gas analysis (pO_2 and pCO_2) was used as a surrogate for hypoxia/hyperoxia and ventilation status.

Conclusions

Our study suggests that pre-hospital oxygenation and ventilation status do not have an impact on survival and neurological outcome in patients with isolated severe TBI. However, our data should be interpreted with caution due to the small sample size. Further prospective and randomized studies in patients with isolated TBI are likely to be helpful to determine the correlation between oxygenation and ventilation status on outcome in patients with isolated severe TBI.

Pre-hospital ventilation should be optimized by maintaining arterial pO_2 and pCO_2 at normal levels (100-200 mmHg and 35-45 mmHg respectively). This could be achieved by an adjustment of ventilator parameters according to continuous $petCO_2$ measurements or by using arterial blood analysis in the pre-hospital arena.

REFERENCES

1. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216-22.
2. The Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Joint Section on Neurotrauma and Critical Care; AANS/CNS. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. J Neurotrauma 2007;24:S37-S44.
3. Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM, Bullock R. Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. J Neurosurg 1999;91:1-10.
4. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR. Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. J Neurosurg 2004;101:435-44.
5. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Arch Surg 2012;147:1042-6.
6. Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma 2009;26:2217-23.
7. Murray JA, Demetriades D, Berne TV, Stratton SJ, Cryer HG, Bongard F, et al. Prehospital intubation in patients with severe head injury. J Trauma 2000;49:1065-70.
8. Davis DP, Peay J, Sise MJ, Vilke GM, Kennedy F, Eastman AB, et al. The impact of prehospital intubation on outcome in moderate to severe traumatic brain injury. J Trauma 2005;58:933-9.
9. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75:731-9.
10. Pepe PE, Raedler C, Lurie KG, Wiggintoon JG. Emergency ventilator management in severe hemorrhagic states: elemental or detrimental? J Trauma 2003;54:1048-55.
11. Stocchetti N, Furlan A, Volta F. Hypoxia and arterial hypotension at the accident scene in head injury. J Trauma 1996;40:764-67.
12. Chi JH, Knudson MM, Vassar MJ, McCarthy MC, Shapiro MB, Mallet S, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: A prospective multicenter study. J Trauma 2006;61:1134-41.
13. Chang JJ, Youn TS, Benson D, Mattick H, Andrade N, Harper CR, et al. Physiologic and functional outcome correlates of brain tissue hypoxia in traumatic brain injury. Crit Care Med 2009; 37:283-90.
14. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO2 to outcome after severe head injury. Crit Care Med 1998;26:1576-81.
15. Zhou Z, Daugherty WP, Sun D, Levasseur JE, Altememi N, Hamm RJ, et al. Protection of mitochondrial function and improvement in cognitive recovery in rats treated with hyperbaric oxygen following lateral fluid percussion injury. J Neurosurg 2007;106:687-94.
16. Diringer MM, Aiyagari V, Zazulia AR, Videen TO, Powers WJ. Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury. J Neurosurg 2007;106:526-9.
17. Rangel-Castilla L, Rivera Lara L, Gopinath S, Swank PR, Valadka A, Robertson C. Cerebral hemodynamic effects of acute hyperoxia and hyperventilation after severe traumatic brain injury. J Neurotrauma 2010;27:1853-63.
18. Bakowitz M, Bruns B, McCunn M. Acute lung injury and the acute respiratory distress syndrome in the injured patient. Scand J Trauma Resusc Emerg Med 2012;20:54.
19. Rincon F, Ghosh S, Dey S, Maltenfort M, Vibbert M, Urtecho J, et al. Impact of acute lung injury and acute respiratory distress syndrome after traumatic brain injury in the United States. Neurosurgery 2012;71:795-803.
20. Wang HE, Peitzman AB, Cassidy LD, Adelson PA, Yealy DM. Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. Ann Emerg Med 2004;44:439-50.
21. Eckstein M, Chan L, Schneir A, Palmer R. Effect of prehospital advanced life support on outcomes of major trauma patients. J Trauma 2000;48:643-8.
22. Davis DP, Dunford JV, Poste JC, Ochs M, Holbrook T, Fortlage D, et al. The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. J Trauma 2004;57:1-8.
23. Wang HE, Balasubramani GK, Cook LJ, Lave JR, Yealy DM. Out-of-hospital endotracheal intubation experience and patients outcomes. Ann Emerg Med 2010;55:527-37.
24. Davis DP, Peay J, Sise MJ, Kennedy F, Simon F, Tominaga G, et al. Prehospital airway and ventilation management: A trauma score and injury severity score-based analysis. J Trauma 2010; 69:294-301.
25. Sloane C, Vilke GM, Chan TC, Hayden SR, Hoyt DB, Rosen P. Rapid sequence intubation in the field versus hospital in trauma patients. J Emerg Med 2000;19:259-64.
26. Katz SH, Falk JL. Misplaced endotracheal tubes by paramedics in an urban emergency medical services system. Ann Emerg Med 2001;37:32-7.

27. Dunford JV, Davis DP, Ochs M, Doney M, Hoyt DB. Incidence of transient hypoxia and pulse rate reactivity during paramedic rapid sequence intubation. Ann Emerg Med 2003;42:721-8.
28. Davis DA, Idris AH, Sise MJ, Kennedy F, Eastman AB, Velky T, et al. Early ventilation and outcome in patients with moderate to severe traumatic brain injury. Crit Care Med 2006;34:1202-8.
29. Dumont TM, Visioni AJ, Rughani AI, Tranmer BI, Crookes B. Inappropriate prehospital ventilation in severe traumatic brain injury increases in hospital mortality. J Neurotrauma 2010; 27:1233-41.
30. Warner KJ, Cuschieri J, Copass MK, Jurkovich GJ, Bulger EM. The impact of prehospital ventilation on outcome after severe traumatic brain injury. J Trauma 2007;62:1330-6.
31. Matta B, Strebel S, Lam A. Effect of the Valsalva maneuver on intracranial hypertension. J Neurosurg Anesthesiol 1994;6:280-3.
32. The Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Joint Section on Neurotrauma and Critical Care; AANS/CNS. Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation. J Neurotrauma 2007;24:S87-S90.
33. Davis DP, Dunford JV, Ochs M, Park K, Hoyt DB. The use of quantitavive end-tidal capnometry to avoid inadvertent severe hyperventilation in patients with head injury after paramedic rapid sequence intubation. J Trauma 2004;56:808-14.
34. Thomas FO, Hoffman TL, Handrahan DL, Crapo RO, Snow G. The measure of treatment agreement between portable and laboratory blood gas measurements in guiding protocol-driven ventilator management. J Trauma 2009;67:303-13.