Ineffective Effort in Patients With Acute Brain Injury Undergoing Invasive Mechanical Ventilation

Xu-Ying Luo, Xuan He, Yi-Min Zhou, Jian-Fang Zhou, Guang-Qiang Chen, Hong-Liang Li, Yan-Lin Yang, Linlin Zhang, and Jian-Xin Zhou

BACKGROUND: Ineffective effort (IE) is a frequent patient-ventilator asynchrony in invasive mechanical ventilation. This study aimed to investigate the incidence of IE and to explore its relationship with respiratory drive in subjects with acute brain injury undergoing invasive mechanical ventilation. METHODS: We retrospectively analyzed a clinical database that assessed patient-ventilator asynchrony in subjects with acute brain injury. IE was identified based on airway pressure, flow, and esophageal pressure waveforms collected at 15-min intervals 4 times daily. At the end of each data set recording, airway-occlusion pressure ($P_{0.1}$) was determined by the airway occlusion test. IE index was calculated to indicate the severity of IE. The incidence of IE in different types of brain injuries as well as its relationship with $P_{0.1}$ was determined. RESULTS: We analyzed 852 data sets of 71 subjects with $P_{0.1}$ measured and undergoing mechanical ventilation for at least 3 d after enrollment. IE was detected in 688 (80.8%) data sets, with a median index of 2.2% (interquartile range 0.4–13.1). Severe IE (IE index ≥ 10%) was detected in 246 (28.9%) data sets. The post craniotomy for brain tumor and the stroke groups had higher median IE index and lower $P_{0.1}$ compared with the traumatic brain injury group (2.6% [0.7–9.7] vs 2.7% [0.3–21] vs 1.2% [0.1–8.5], *P* = .002; 1.4 [1–2] cm H_2O vs 1.5 [1–2.2] cm H_2O vs 1.8 [1.1–2.8] cm H_2O, *P* = .001). Low respiratory drive ($P_{0.1}$ < 1.14 cm H_2O) was independently associated with severe IE in the expiratory phase (IEE) even after adjusting for confounding factors by logistic regression analysis (odds ratio 5.18 [95% CI 2.69–10], *P* < .001). CONCLUSIONS: IE was very common in subjects with acute brain injury. Low respiratory drive was independently associated with severe IEE. *Key words: ineffective effort; respiratory drive; acute brain injury; patient-ventilator asynchrony; mechanical ventilation.* [Respir Care 2023;68(9):1202–1212. © 2023 Daedalus Enterprises]

Introduction

Ineffective effort (IE) refers to a patient's inspiratory effort failing to trigger a ventilator breath, a common type of patient-ventilator asynchrony in critically ill patients undergoing mechanical ventilation.[1-3] It could occur in both inspiratory and expiratory phases, possibly resulting in muscle atrophy, contractile dysfunction, and eccentric contractions of the diaphragm, therefore inducing muscle injury.[4,5] Severe IE has been found to be associated with poor outcomes, including decreased weaning success, longer duration of mechanical ventilation, longer stay in the ICU, and higher mortality.[6-8] However, its incidence is remarkably varied because different populations were studied and different detection methods were used.[8-10]

Previous studies showed that dynamic hyperinflation, intrinsic PEEP, and low respiratory drive might promote IE.[1,8,11] Dynamic hyperinflation and intrinsic PEEP, as common etiologies of IE in patients with COPD, have been frequently studied.[1,10] Low respiratory drive is mainly attributed to deep sedation and overassistance.[4,12] However, it could also be caused by direct injuries to the respiratory center, including the brain stem and cortex.[13] Few studies have concentrated on the incidence of IE in subjects with acute brain injury.[14]

This retrospective study aimed to assess the incidence of IE in subjects with acute brain injury at the initiation of mechanical ventilation. Esophageal pressure (P_{es}) monitoring was used to facilitate the diagnosis of IE occurring in different respiratory phases. Airway-occlusion pressure ($P_{0.1}$) was used as a marker of respiratory drive, and its relationship with IE was determined.[15] In addition, we also tried to explore the association between opioids/sedatives administration and the incidence of IE in this subject population.

Methods

Study Population

This was a secondary analysis of data collected as a prior prospective observational study investigating patient-ventilator asynchrony in adult subjects with acute brain injuries in the ICU of Beijing Tiantan Hospital, Capital Medical University (ClinicalTrials.gov: NCT03212482). Subjects diagnosed with acute brain injuries and underwent mechanical ventilation were enrolled within 24 h of initiation of mechanical ventilation. Subjects were excluded if they met one of the following criteria: (1) duration of mechanical ventilation was < 72 h; (2) presented with epilepsy; (3) agitation; (4) contraindications for esophageal balloon catheter insertion; (5) evidence of active air leak from the lung that included bronchopleural fistula, pneumothorax, pneumomediastinum, and chest tube; and (6) without spontaneous breathing.

SEE THE RELATED EDITORIAL ON PAGE 1322

The study protocol was approved by the institutional review board of Beijing Tiantan Hospital, Capital Medical University (KY 2017–028-02).

Data Collection

Demographic and clinical data were extracted from electronic medical records, consisting of classification of the brain injury, Glasgow coma scale score at admission, comorbidities, APACHE II score at ICU admission and related clinical data, duration of mechanical ventilation, as well as the length of stay in the ICU.

Subjects were connected to an Avea ventilator (Vyaire Medical, Mettawa, Illinois) after enrollment. Then an esophageal balloon catheter (SmartCath-G catheter, lot 7003300, Vyaire Medical) was placed for P_{es} monitoring and tube feeding simultaneously. The esophageal balloon was placed in the lower two thirds of the intrathoracic esophagus, and the optimal balloon position was determined by the Baydur occlusion test in subjects with spontaneous breathing[16] or by the positive-pressure occlusion test in those without.[17]

QUICK LOOK

Current knowledge

Ineffective effort (IE) is a common patient-ventilator asynchrony in the ICU. Dynamic hyperinflation, intrinsic PEEP, and low respiratory drive caused by deep sedation and overassistance are all risk factors for the high incidence of IE. Severe IE has been shown to be associated with poor outcomes, including prolonged duration of mechanical ventilation, longer stay in the ICU, and higher in-hospital mortality.

What this paper contributes to our knowledge

This study found that IE was frequent in subjects with acute brain injury, especially those with brain tumor and stroke involving the infratentorial region. Both incidences of IE and severe IE were high. Low respiratory drive was independently associated with severe IE in the expiratory phase. However, no relationship between IE in the inspiratory phase and respiratory drive was found.

Airway pressure (P_{aw}), flow, and P_{es} waveforms were collected via a dedicated acquisition system (VOXP Research Data Collector 3.2, Applied Biosignals, Weener, Germany) at a frequency of 100 Hz. The signals were recorded 4 times daily, each for 15 min, and saved as one waveform data set. The waveform collection was conducted for 3 d and stopped in case of separation from the ventilator. End-expiratory occlusion was performed at the end of each recording. For subjects with spontaneous breathing, $P_{0.1}$ was measured and averaged for 5 occlusions to represent the respiratory drive.[15]

Ventilator modes and settings, respiratory parameters, the use of opioids/sedatives and neuromuscular blocking agents, sedation-agitation scale (SAS), and Glasgow coma scale score during each recording were collected. Arterial blood gas analysis was carried out at least once per day for each subject. Ventilator modes and settings, respiratory parameters, and administration of opioids/sedatives were determined by the ICU physicians and remained unchanged during recordings. Investigators were not involved in the treatment of subjects.

Drs Luo, He, Yi-Min Zhou, Jian-Fang Zhou, Chen, Li, Yang, and Zhang are affiliated with Department of Critical Care Medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Dr Jian-Xin Zhou is affiliated with Department of Critical Care Medicine, Beijing Shijitan Hospital, Capital Medical University, Beijing, China.

The authors have disclosed no conflicts of interest.

This work was supported by a grant from the Beijing Municipal Science and Technology Commission (number Z161100000116081). The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Supplementary material related to this paper is available at http://www.rcjournal.com.

Correspondence: Jian-Xin Zhou MD, Department of Critical Care Medicine, Beijing Shijitan Hospital, Capital Medical University, No. 10 Tieyi Road, Yangfangdian, Haidian District, Beijing, 100038, China. E-mail: zhoujx.cn@icloud.com.

DOI: 10.4187/respcare.10596

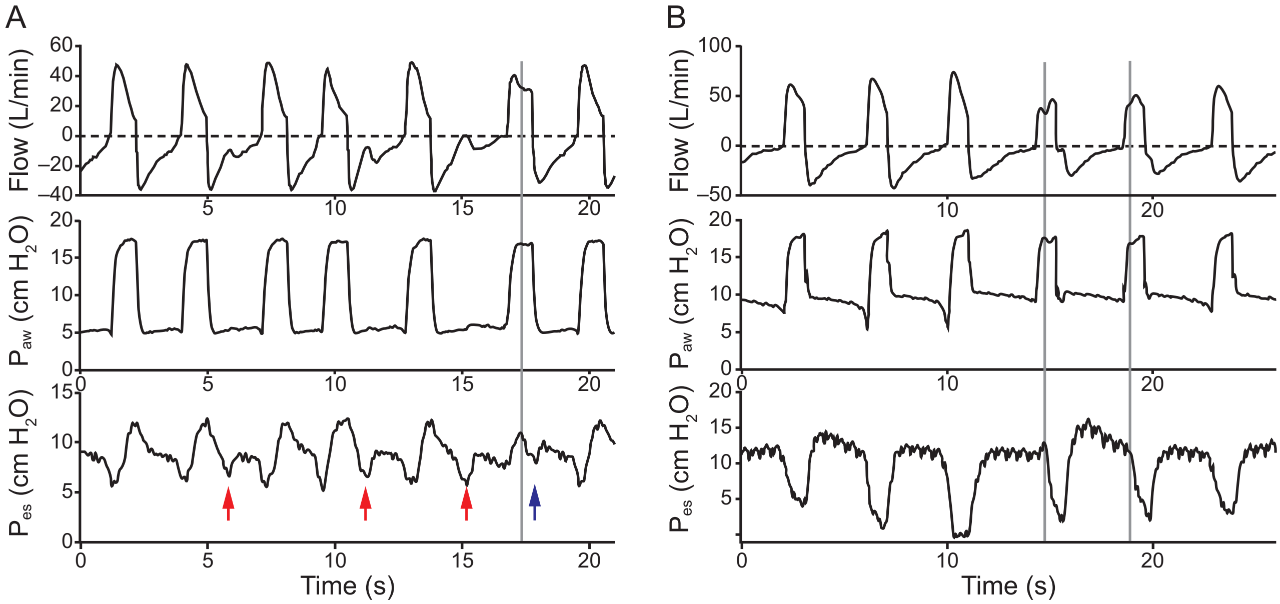

Fig. 1. Flow, airway pressure (P_{aw}), and esophageal pressure (P_{es}) over time during pressure assist/control ventilation showed ineffective efforts (IEs) occurring in mechanical inspiratory and expiratory phases. IE was identified as a decrease in P_{es} associated with a simultaneous increase in flow and/or a decrease in P_{aw} that was not followed by a ventilator cycle. Red arrows indicate ineffective inspiratory effort occurring in mechanical expiratory phase. The blue arrow shows ineffective inspiratory effort occurring in mechanical inspiratory phase, and gray vertical lines indicates the onset of inspiratory efforts. A: IEs in a subject with lower respiratory drive; B: IEs in a subject with higher respiratory drive.

Definition of Ineffective Effort

Patient-ventilator asynchrony was identified by visual inspection of P_{aw}, flow, and P_{es} waveforms. IE was defined as an inspiratory effort, indicated by a decrease in P_{es} associated with a simultaneous increase in flow and/or a decrease in P_{aw}, that was not followed by a ventilator cycle. IE could occur in both mechanical inspiratory phase (IEI) and expiratory phase (IEE).[1,18] The example waveforms are shown in Figure 1. Waveforms were analyzed offline by the 2 investigators (XYL and XH) independently. All breaths were inspected and identified by the 2 investigators. The diagnosis of patient-ventilator asynchrony was confirmed when the 2 investigators made the same decisions. Otherwise, the final decision was made based on a group discussion (HLL, YLY, and JXZ).

IE index was defined as the number of IEs divided by the total number of ventilator cycles and IEs. Severe IE was defined as IE index ≥ 10% based on the data set.[19]

Statistical Analysis

Non-normally distributed continuous variables were described as median (interquartile range) and compared between groups using the Mann-Whitney U test or Kruskal-Wallis analysis-of-variance test with Bonferroni correction. Categorical variables were expressed as proportions and compared across groups using the chi-square test or the Fisher exact test. The predictive ability of $P_{0.1}$ to correctly predict severe IE was assessed by calculating the area under the receiver operating characteristic curve. The statistical analysis was performed using SPSS 21.0 software (IBM, Armonk, New York). $P < .05$ was considered statistically significant.

Results

During the study period (June 2017–July 2019), 264 subjects diagnosed with acute brain injury who underwent mechanical ventilation were screened. In total, 193 subjects were excluded, comprising 104 subjects < 18 y, 55 with a duration of mechanical ventilation < 72 h, 25 with epilepsy, 3 with contraindications for esophageal balloon catheter insertion, and 6 without spontaneous breathing. The remaining 71 subjects with 852 data sets covering 266,229 breaths were analyzed, including stroke (36.6%), traumatic brain injury (TBI, 26.8%), and post craniotomy for brain tumor (36.6%). Subjects with TBI had lower Glasgow coma scale scores and slightly higher APACHE II scores than those with stroke and brain tumor. The characteristics of the cohort are shown in Table 1.

The Incidence of Ineffective Effort

IE was detected in all subjects covering 688 (80.8%) data sets, with a median IE index of 2.2% (0.4–13.1). Severe IE (IE index ≥ 10%) was detected in 48 (67.6%)

Table 1. Comparison of Characteristics Among Different Classification of Brain Injuries

Category	Post Craniotomy for Brain Tumors ($n = 26$)	TBI ($n = 19$)	Stroke ($n = 26$)	P
Age, y	53 (44–62)	53 (37–69)	60 (38–67)	.85
Male	17 (65.4)	15 (78.9)	17 (65.4)	.55
APACHE II at ICU admission	16 (13–20)	21 (17–25)	19 (14–21)	.02
Glasgow coma scale at inclusion	11 (9–11)	6 (5–7)	11 (6–11)	< .001
Infratentorial lesions	17 (65.4)	2 (10.5)	12 (46.2)	.001
P_{aO_2}/F_{IO_2} at inclusion, mm Hg	211 (166–302)	260 (180–338)	230 (164–351)	.85
P_{aCO_2} at inclusion, mm Hg	38 (34–42)	42 (36–46)	37 (30–42)	.14
Intrinsic PEEP cm H_2O	0.7 (0–1.5)	1.3 (0–3.5)	0.9 (0–1.8)	< .001
Comorbidity				
COPD	0	2 (10.5)	0	.069
Hypertension	11 (42.3)	3 (15.8)	13 (50)	.056
Diabetes mellitus	3 (11.5)	3 (15.8)	7 (26.9)	.34
Coronary heart disease	3 (11.5)	2 (10.5)	4 (15.4)	> .99
Outcomes				
ICU mortality	1 (3.8)	2 (10.5)	5 (19.2)	.26
In-hospital mortality	2 (7.7)	2 (10.5)	6 (23.1)	.32
For subjects alive at hospital discharge ($n = 61$)	$n = 24$	$n = 17$	$n = 20$	
Duration of mechanical ventilation, d	8 (5–17)	10 (6–21)	7 (5–15)	.34
Successful weaning	20 (76.9)	15 (88.2)	19 (73.1)	.94
LOS in ICU, d	16 (10–25)	30 (10–43)	16 (8–21)	.13
LOS in hospital, d	38 (26–48)	30 (24–46)	34 (23–40)	.63

Data are presented as n (%) or median (interquartile range).
TBI = traumatic brain injury
APACHE II = Acute Physiology and Chronic Health Evaluation II
LOS = length of stay

subjects covering 246 (28.9%) data sets, with a median IE index of 26.7% (16.8–40).

Data sets with severe IE had lower $P_{0.1}$, lower breathing frequency, lower minute ventilation, and higher P_{aCO_2} level than those without (Fig. 2). They had higher Glasgow coma scale scores and received fewer opioids/sedatives administration. No significant differences were found in ventilator mode, tidal volume, and SAS score between data sets with and without severe IE. Subgroup analysis of 543 data sets with no administration of opioids/sedatives yielded similar results (Table S1, see related supplementary materials at http://www.rcjournal.com).

Factors Associated With Ineffective Effort

Brain injury. The post craniotomy for brain tumor and the stroke groups had higher IE index, lower $P_{0.1}$, and lower breathing frequency compared with the TBI group (Fig. 3). No significant differences were found in tidal volume (8.6 [7–9.9] mL/kg vs 7.9 [7.1–9.7] mL/kg vs 8 [7.2–9.3] mL/kg, $P = .08$) and minute ventilation (8.7 [7.2–10.3] L/min vs 8.8 [7.2–10.4] L/min vs 8.8 [7.4–12] L/min, $P = .033$) between groups after Bonferroni correction. Severe IE was more common in the stroke group than the post craniotomy for brain tumor and the TBI groups (38.1% vs 24.4% vs 22.4%, $P < .001$).

The post craniotomy for brain tumor and the stroke groups also had a higher proportion of infratentorial lesions than the TBI group (65.4% vs 46.2% vs 10.5%, $P = .001$). Subjects with infratentorial lesions had higher IE index, lower $P_{0.1}$, lower breathing frequency, but larger tidal volume than those with supratentorial lesions (Fig. 4). In addition, they also had higher Glasgow coma scale score, higher SAS score, higher P_{aCO_2}, and lower minute ventilation than those with supratentorial lesions (11 [10–11] vs 7 [5–10], $P < .001$; 4 [3–4] vs 3 [2–3], $P < .001$; 40 [36–45] cm H_2O vs 38 [34–42] cm H_2O, $P = .002$; 8.4 [6.9–9.9] L/min vs 9.1 [7.6–11.2] L/min, $P < .001$, respectively). For subjects who did not receive opioids/sedatives, similar results were obtained.

Administration of opioids/sedatives. No-drugs group had higher IE index, lower $P_{0.1}$, and lower minute ventilation compared with opioids only and the opioids + sedatives groups. No significant differences were found in IE index, $P_{0.1}$, tidal volume, and minute ventilation between no drugs and sedatives only groups (Fig. 5). No drugs and sedative only groups had higher median SAS scores compared with opioids only and opioids + sedatives groups (3 [3–4] vs 3 [3–4] vs 3 [2–4] vs 3 [2–4], $P < .001$). No significant differences in Glasgow coma scale score were found among sedative only, opioids only, opioids + sedatives, and no

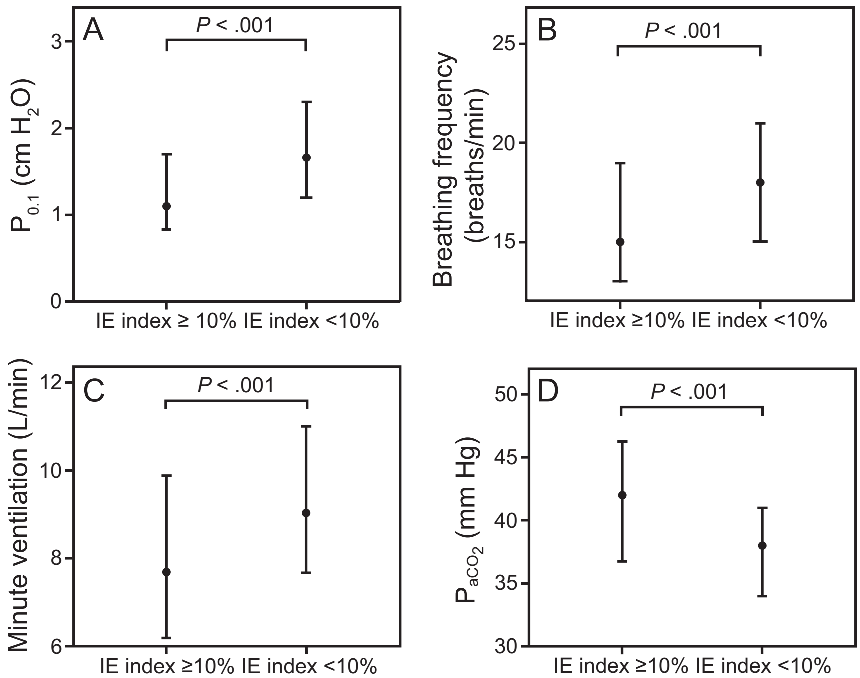

Fig. 2. Data sets with severe ineffective effort (IE) (IE index ≥ 10%) had lower airway-occlusion pressure, lower breathing frequency, lower minute ventilation, and higher P_{aCO_2} level than those without. $P_{0.1}$ = airway-occlusion pressure.

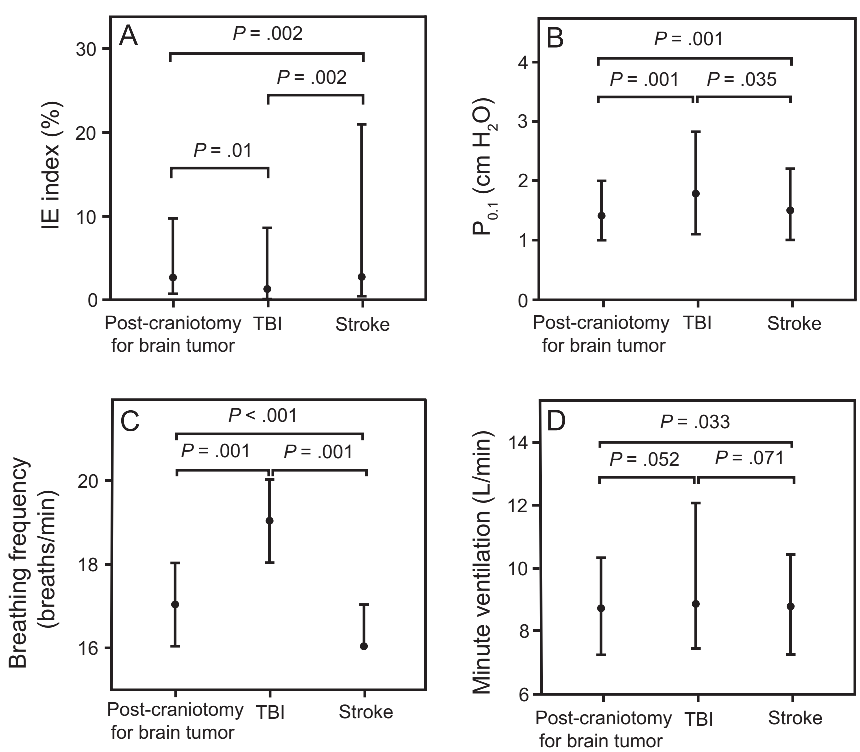

Fig. 3. Comparison of ineffective effort (IE) index, airway-occlusion pressure ($P_{0.1}$), breathing frequency, and minute ventilation among different brain injury groups. Post craniotomy for brain tumor and the stroke groups had higher IE index (A), lower $P_{0.1}$ (B), and lower breathing frequency (C) than the traumatic brain injury (TBI) group. They also had relatively lower minute ventilation (D) than the TBI group, although no significant differences were found between groups after Bonferroni correction.

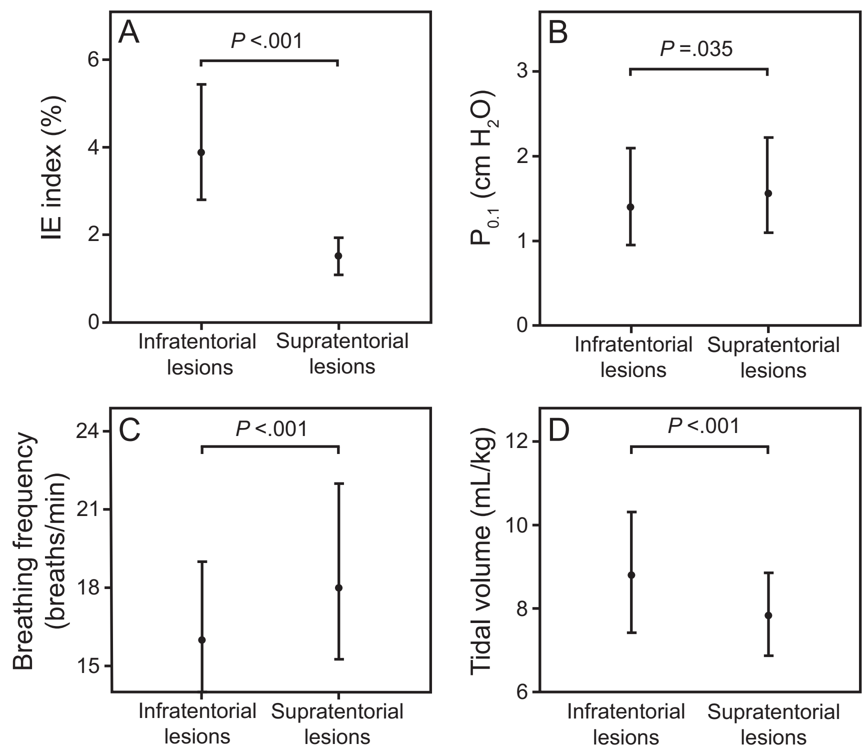

Fig. 4. Comparison of ineffective effort (IE) index, airway-occlusion pressure ($P_{0.1}$), breathing frequency, and tidal volume between infratentorial lesions and supratentorial lesions groups. Infratentorial lesions group had higher IE index (A), lower $P_{0.1}$ (B), lower breathing frequency (C), and larger tidal volume (D) than supratentorial lesions group. IE = ineffective effort; $P_{0.1}$ = airway-occlusion pressure.

drugs groups (8 [6–11] vs 8 [5–11] vs 9 [6–11] vs 10 [7–11], respectively, $P = .25$).

Subjects in the TBI group received more opioids/sedatives administration, especially opioids + sedatives, compared with the stroke and the post craniotomy for brain tumor groups ($P < .001$) (Fig. 6). They also had lower SAS scores than the stroke and the post craniotomy for brain tumor groups (3 [2–3] vs 3 [2–4] vs 4 [3–4], $P < .001$).

Ineffective Effort in Inspiratory and Expiratory Phases

IEI occurred in 443 (52%) data sets and accounted for 24% of all IEs. In comparison, IEE occurred in 606 (64%) data sets, accounting for 76% of all IEs. IEE was more frequent than IEI in our subject group.

According to different IE types detected, 852 data sets were divided into 4 groups, including IEI only (9.6%), IEE only (28.8%), IEI + IEE (42.4%), and no IE (19.2%) groups. The IEE only group had higher IE index, lower $P_{0.1}$, lower minute ventilation, and lower breathing frequency than no IE group (Fig. 6). Tidal volume and P_{aCO_2} level between IEE only and no IE groups were comparable (Table S2, see related supplementary materials at http://www.rcjournal.com). The IEI only group had a larger tidal volume than no IE group (8.8 [7.6–10.3] mL/kg vs 7.8 [6.7–8.7] mL/kg, $P < .001$). $P_{0.1}$ and minute ventilation between IEI only and no IE groups were comparable (Fig. 7). Similar results were obtained for subjects who did not receive opioids/sedatives (Table S2).

Furthermore, $P_{0.1}$ had a good predictive ability for severe IEE (IEE incidence $\geq$ 10%). The area under the curve for severe IEE was 0.78 (95% CI 0.74–0.82, $P < .001$), and the best cutoff point was 1.14 cm H_2O (sensitivity 71.7%, specificity 71.3%). Low respiratory drive ($P_{0.1} < 1.14$ cm H_2O) was independently associated with severe IEE, even after adjusting for tidal volume, breathing frequency, PEEP, inspiratory triggering type, P_{aCO_2}, P_{aO_2}/F_{IO_2}, Glasgow coma scale score, classification of acute brain injuries, opioids/sedatives administration, and SAS score (odds ratio 5.18 [95% CI 2.69–10], $P < .001$).

Ineffective Effort and Outcomes

Subjects with $\geq$ 4 data sets of severe IE had a longer duration of mechanical ventilation and a longer stay in hospital than those with < 4 data sets of severe IE (13 [6–21] d vs 6 [5–12] d, $P = .040$; 39 [30–51] d vs 30 [23–39] d, $P = .01$). No significant differences were found in the length of stay in ICU, ICU mortality, and in-hospital mortality between the two groups (20 [10–35] d vs 16 [10–23] d, $P = .21$; 11.1% vs 11.4%, $P > .99$; 18.5% vs 11.4%, $P = .49$, respectively).

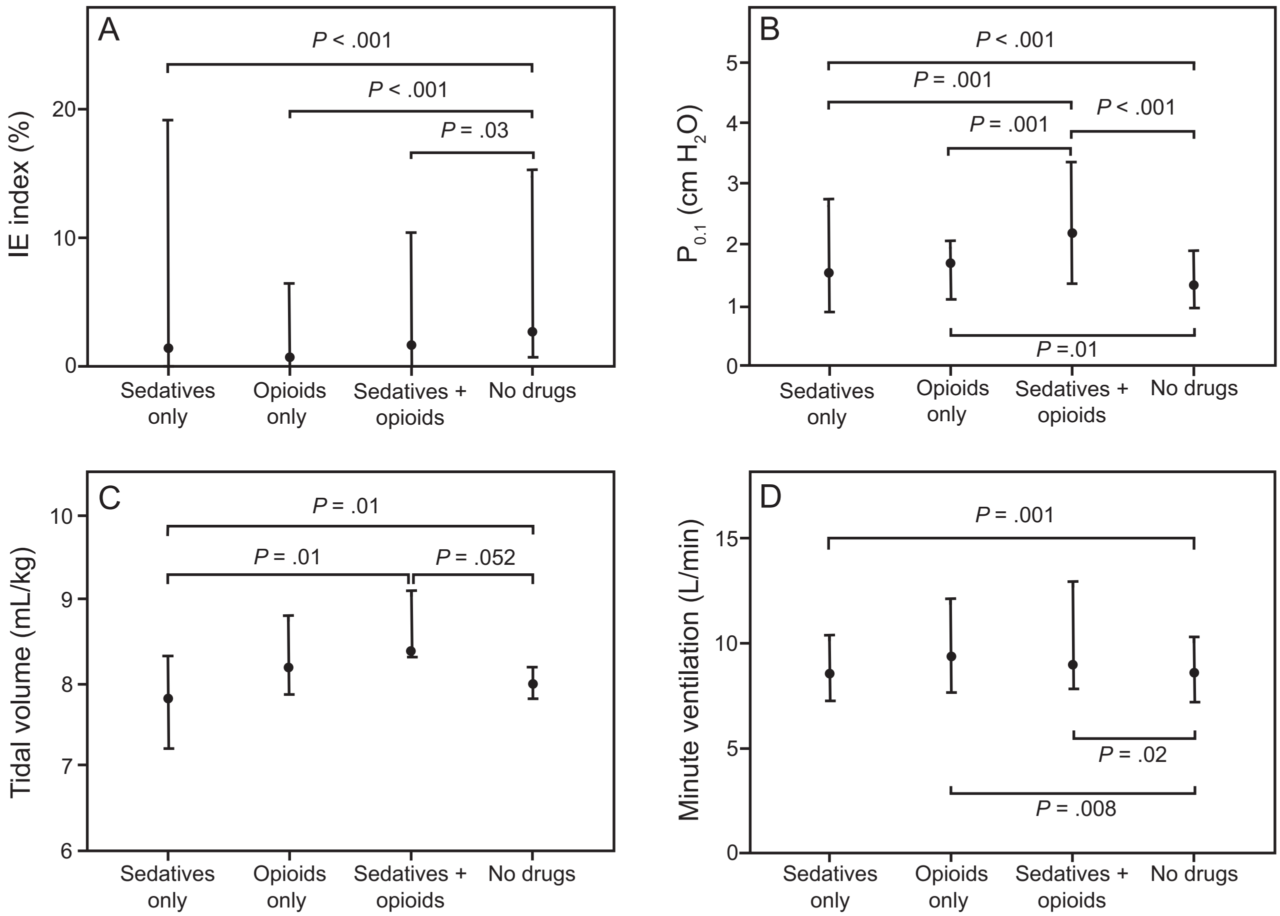

Fig. 5. Comparison of ineffective effort (IE) index, airway-occlusion pressure ($P_{0.1}$), tidal volume, and minute ventilation and among different analgesia/sedation strategies. The no drugs group had higher IE index (A), lower $P_{0.1}$ (B), and lower minute ventilation (D) compared with the opioids only and the opioids + sedatives groups even after Bonferroni correction. The no drugs group also had relatively smaller tidal volume (C) than the opioids + sedatives group, although no significant difference was found after Bonferroni correction. No significant differences were found in IE index (A), $P_{0.1}$ (B), tidal volume (C), and minute ventilation (D) between the sedatives only and the no drugs groups either.

Furthermore, subjects with prolonged mechanical ventilation (> 7 d) had lower $P_{0.1}$ and higher incidence of IEE, but a lower incidence of IEI, compared with those receiving mechanical ventilation < 7 d (1.3 [0.9–1.9] cm H_2O vs 1.7 [1.2–2.6] cm H_2O, $P < .001$; 1.7% [0.2–12.2] vs 0.9% [0–4.9], $P < .001$; 0 [0–0.9] vs 0.4% [0–1.3], $P = .02$, respectively). There was a trend that IE index increased over 3 d in subjects with prolonged mechanical ventilation (> 7 d) but decreased in those undergoing mechanical ventilation for < 7 d, although the difference was not significant (Fig. S1, see related supplementary materials at http://www.rcjournal.com).

Discussion

The main findings of this study could be summarized as follows: (1) IE was detected in all subjects covering 80.8% of data sets, with severe IE in 48 (67.6%) subjects covering 28.9% of data sets; (2) the post craniotomy for brain tumor and the stroke groups had higher IE index and lower $P_{0.1}$ compared with the TBI group; (3) no-drugs group had higher IE index and low $P_{0.1}$ than opioids-only and opioids-plus-sedatives groups; and (4) low respiratory drive ($P_{0.1} < 1.14$ cm H_2O) was independently associated with severe IEE.

Brain Injury and Ineffective Effort

IE has been reported to be the most frequent asynchrony in critically ill patients, with incidence varying from 11–80% depending on the population studied. A high incidence of IE has been mainly found in patients with COPD or those receiving deep sedation, resulting in decreased inspiratory drive.[6,10,11,20]

Our study found that IE was detected in 80.8% of data sets. Severe IE was detected in 28.9% of data sets, which was comparable to that in subjects with COPD.[10,11] However,

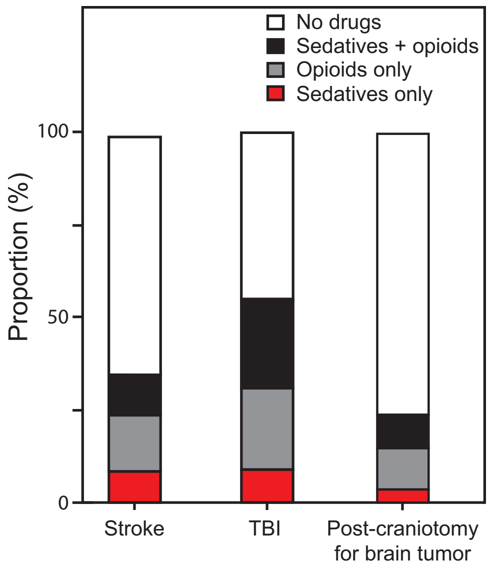

Fig. 6. The proportion of sedatives only, opioids only, sedatives + opioids, and no drugs administration among post craniotomy for brain tumor, traumatic brain injury (TBI), and stroke groups. Subjects in the TBI group received more opioids/sedatives administration, especially opioids + sedatives, compared with post craniotomy for brain tumor and the stroke groups (55.3% vs 24% vs 31.6%, 22.8% vs 8.3% vs 9.9%, $P < .001$).

only 2 (2.8%) subjects with COPD were enrolled in this study. The median intrinsic PEEP was 0.9 cm H_2O (0–1.9), which was also < that in subjects with COPD.[12,21] A high incidence of IE could be attributed to low respiratory drive caused by acute brain injuries. Compared with the TBI group, the post craniotomy for brain tumor and the stroke groups had higher IE index, lower $P_{0.1}$, and a higher proportion of infratentorial lesions, including lesions in the brain stem, cerebellum, or both. The respiratory control centers are located in the brain stem, including the rhythmicity center in the medulla (dorsal and ventral respiratory group) generating respiration and the pontine pneumotaxic center adjusting the rate and depth of respiration.[13,22] Thus, subjects with infratentorial lesions were at a higher risk of impairment of the respiratory center. Low respiratory drive resulting from impairment of the respiratory center was characterized by a slightly larger tidal volume, lower breathing frequency rate, lower minute ventilation, and a higher P_{aCO_2} level, which differed from the decreased respiratory drive due to excessive sedation, characterized by the reduced tidal volume, whereas breathing frequency did not change.[6] Moreover, the incidence of IE was relatively higher in the TBI group than that in previous studies in general ICU subjects.[2,21] Although the respiratory rhythm was generated by the brain stem, it could also be influenced by higher centers in the brain including the cerebral cortex.[13,22] Thus, either cortical or brain stem injuries might affect respiratory drive and lead to a high incidence of IE.

Moreover, different detection methods could also influence the incidence of IE. P_{aw} and flow waveforms were reported as the most convenient methods to detect IE, whereas their diagnostic accuracies were unsatisfactory.[23,24] Recently, automated systems based on ventilator P_{aw} and flow waveforms have been developed to detect patient-ventilator asynchronies at the bedside, whereas they could not identify IE occurring in either the inspiration phase or the early expiration phase.[25,26] P_{es} monitoring combined with P_{aw} and flow waveforms could promote recognition of IE.[5,27]

Analgesia/Sedation and Ineffective Effort

Analgesia and sedation may promote or reduce the incidence of IE depending on the administrated doses. Appropriate analgesia and sedation may alleviate patients' pain and anxiety and improve patient-ventilator synchrony; however, excessive doses may depress respiratory drive and lead to a higher rate of IE.[6] de Haro et al[20] demonstrated a lower incidence of IE in the sedatives + opioids group than in the no drugs group. They found opioid dose was inversely associated with the incidence of IE; sedative dose was directly associated with the incidence of IE and a lower level of consciousness; however, Dzierba et al[28] reported no association between the sedation level or pain control and the respiratory drive.

In the present study, the opioids-only and the sedatives + opioids groups had lower IE index than the no drugs group, which was in agreement with de Haro et al findings. However, the opioids only group had lower SAS scores and a relatively lower level of consciousness than the sedatives only and no drugs groups, which seemed to be paradoxical. Opioids administration was more frequent in the TBI group compared with that in the stroke and the post craniotomy for brain tumor groups, both of which had higher Glasgow coma scale scores than TBI. Physicians might tend to prescribe more opioids for patients with TBI, who mainly suffered from severe pain and stress, but tolerated fewer brain stem injuries. However, for patients in the post craniotomy for brain tumor and the stroke groups who were at a higher risk of impairment of respiratory center, physicians prescribed fewer opioids/sedatives. Thus, lower IE index in opioids only and opioids + sedatives groups could be attributed to a larger proportion of subjects with TBI who had relatively higher $P_{0.1}$. Although more opioids/sedatives were administrated, deep sedation was not common in the TBI group, with a median SAS score of 3 (2–3).

Ineffective Effort in Inspiratory and Expiratory Phases

About a quarter of IE occurred in the inspiratory phase, which was similar to Thille et al[1] findings. No significant differences were found in $P_{0.1}$, minute ventilation, P_{aCO_2},

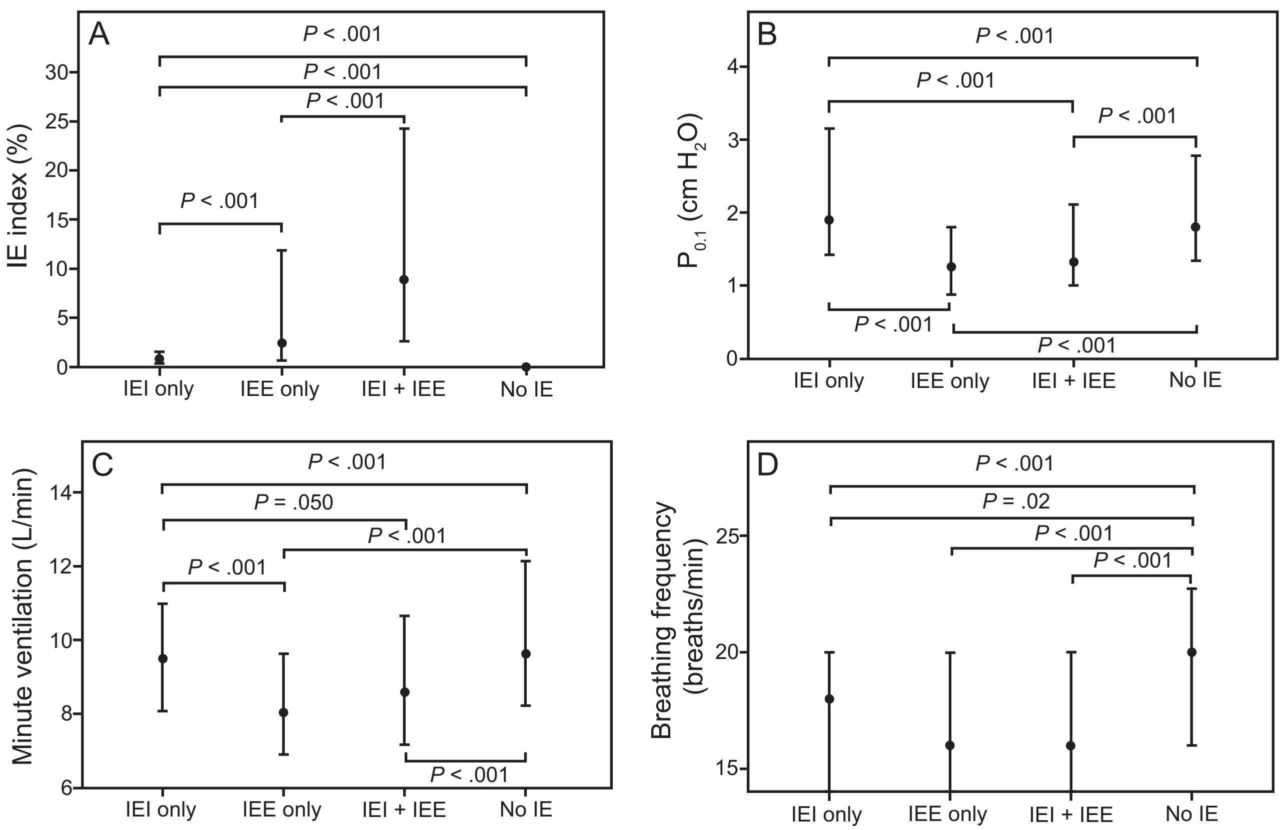

Fig. 7. Comparison of ineffective effort (IE) index, airway-occlusion pressure ($P_{0.1}$), minute ventilation, and breathing frequency among ineffective effort occurring during inspiratory phase (IEI), ineffective triggering occurring during expiratory phase (IEE), IEI + IEE, and no IE groups. The IEE only group had higher IE index (A), lower $P_{0.1}$ (B), lower minute ventilation (C), and lower breathing frequency (D) than the no IE group. The IEI only group had higher IE index (A) and lower breathing frequency (D) than the no IE group; $P_{0.1}$ (B) and minute ventilation (C) between the IEI only and the no IE groups were similar. IE = ineffective effort; IEI = IE during inspiratory phase; IEE = IE during expiratory phase; $P_{0.1}$ = airway-occlusion pressure.

Glasgow coma scale score, and SAS score between the IEI-only and the no IE groups. However, the IEI only group received fewer opioids/sedatives than the no IE group. IEI usually occurred during periods of subject-triggered breaths, which was irregular and did not keep the same characteristics of phase lag, whereas reverse triggering usually occurred during passive ventilation in a repetitive and consistent manner.[29] An expiratory occlusion could differentiate IE from reverse triggering.[30] We speculated that IEI might be caused by pain or anxiety rather than low respiratory drive. Considering the low incidence of IEI in this study, we could not draw any concrete conclusions, and additional studies should be conducted in the future.

IEE accounted for the majority of IE in the present study. The IEE only group had decreased respiratory drive characterized by lower $P_{0.1}$, lower minute ventilation, and relatively higher P_{aCO_2} than no-IE group. Low respiratory drive ($P_{0.1}$ < 1.14 cm H_2O) was independently associated with severe IEE. Furthermore, subjects with prolonged mechanical ventilation (> 7 d) had lower $P_{0.1}$, a higher incidence of IEE, but a lower incidence of IEI compared with those undergoing mechanical ventilation for < 7 d. Thus, we speculate that prolonged mechanical ventilation might result from the low respiratory drive. Dzierba et al[28] reported that $P_{0.1}$ of 0.5–1.5 cm H_2O was associated with a greater number of ventilator-free days. Their study was conducted in medical, surgical, and cardiac ICUs, where half of the participants had ARDS, whose respiratory drive might be mainly affected by the severity of diseases rather than impairment of the respiratory center.

Ineffective Effort and Outcomes

Previous studies showed that severe IE was associated with longer duration of mechanical ventilation, longer ICU and hospital stay, although no causal relationship was proved.[7,19,31] Other studies found no association between the severity of IE and outcomes.[3,8] In the present study, subjects with more data sets of severe IE (≥ 4 data sets) had longer duration of mechanical ventilation and longer stays in the hospital. There was also a trend that subjects with prolonged mechanical ventilation (> 7 d) had an increased IE index on the third day, whereas those receiving mechanical ventilation for < 7 d had a decreased IE index on the third day. Thus, we speculate that IE that occurred in the initiation of mechanical ventilation and resolved immediately may have no association with outcomes; otherwise, it may indicate unresolved clinical problems and longer duration of mechanical ventilation.[4] Decreasing pressure support and tidal volume or applying external PEEP to avoid dynamic hyperinflation and consequently reducing IE[10,12] may not help reduce IE in this population who have respiratory center injuries. Adequate ventilation support until recovery of the respiratory drive may be necessary, which deserves further study in the future.

There are some limitations in this study. First, this was a single-center retrospective study, and its clinical procedures might differ from others. The number of subjects receiving craniotomy for brain tumors was higher than in other studies, and two thirds of the brain tumor were in the infratentorial region; thus, they were at a higher risk of impairment of the respiratory center. Therefore, our findings may be not generalizable to other units. Second, we only analyzed data sets of 3 d after enrollment, which could not reflect the whole period of mechanical ventilation or the weaning period. Our study suggested that for subjects with acute brain injuries the impairment of the respiratory center could be one of the reasons that causes decrease in respiratory drive and severe IEE at the initiation of mechanical ventilation. Third, although IEI occurring during periods of subject-triggered breaths did not fit the understood definition of reverse triggering, we did not perform an expiratory occlusion to rule out reverse triggering when IEs were detected. Fourth, the SAS used to assess sedation depth may be oversimplified. Although we did not analyze the effects of the doses of opioids/sedatives on sedation depth, respiratory drive, or the incidence of IE, subgroup analysis was performed among data sets with no opioids/sedatives administration, and it yielded similar results. Furthermore, $P_{0.1}$, used as a marker of respiratory drive, could be affected by respiratory muscles; hence, we excluded subjects with neuromuscular diseases. Finally, subjects were enrolled as soon as the initiation of mechanical ventilation; thus, they were less likely to be affected by prolonged mechanical ventilation–caused respiratory muscle weakness.

Conclusions

IE was found very frequently in acute brain-injured subjects. The post craniotomy for brain tumor and the stroke groups had higher incidence of IE due to low respiratory drive, resulting from impairment of the respiratory center, characterized by lower breathing frequency, lower minute ventilation, and higher P_{aCO_2} level. IE index in no drugs group was higher than that in the opioids only and the opioids + sedatives groups. Low respiratory drive ($P_{0.1} < 1.14$ cm H_2O) was independently associated with severe IEE. However, no relationship between IEI and respiratory drive was found. Pathophysiological mechanisms of different respiratory center injuries need further study in the future.

REFERENCES

1. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006;32(10):1515-1522.
2. Vaporidi K, Babalis D, Chytas A, Lilitsis E, Kondili E, Amargianitakis V, et al. Clusters of ineffective efforts during mechanical ventilation: impact on outcome. Intensive Care Med 2017;43(2):184-191.
3. Robinson BR, Blakeman TC, Toth P, Hanseman DJ, Mueller E, Branson RD. Patient-ventilator asynchrony in a traumatically injured population. Respir Care 2013;58(11):1847-1855.
4. Pham T, Telias I, Piraino T, Yoshida T, Brochard LJ. Asynchrony consequences and management. Crit Care Clin 2018;34(3):325-341.
5. Esperanza JA, Sarlabous L, de Haro C, Magrans R, Lopez-Aguilar J, Blanch L. Monitoring asynchrony during invasive mechanical ventilation. Respir Care 2020;65(6):847-869.
6. Vaschetto R, Cammarota G, Colombo D, Longhini F, Grossi F, Giovanniello A, et al. Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 2014;42(1):74-82.
7. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, et al. Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med 2015;41(4):633-641.
8. Rolland-Debord C, Bureau C, Poitou T, Belin L, Clavel M, Perbet S, et al. Prevalence and prognosis impact of patient-ventilator asynchrony in early phase of weaning according to 2 detection methods. Anesthesiology 2017;127(6):989-997.
9. Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? Respir Care 2011;56(1):25-38.
10. Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M. Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. Chest 1997;112 (6):1592-1599.
11. de Wit M, Pedram S, Best AM, Epstein SK. Observational study of patient-ventilator asynchrony and relationship to sedation level. J Crit Care 2009;24(1):74-80.
12. Thille AW, Cabello B, Galia F, Lyazidi A, Brochard L. Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure support ventilation. Intensive Care Med 2008;34(8):1477-1486.
13. Williams K, Hinojosa-Kurtzberg M, Parthasarathy S. Control of breathing during mechanical ventilation: who is the boss? Respir Care 2011;56(2):127-136.
14. Luo XY, He X, Zhou YM, Wang YM, Chen JR, Chen GQ, et al. Patient-ventilator asynchrony in acute brain-injured patients: a prospective observational study. Ann Intensive Care 2020;10(1):144.
15. Telias I, Damiani F, Brochard L. The airway-occlusion pressure ($P_{0.1}$) to monitor respiratory drive during mechanical ventilation: increasing awareness of a not-so-new problem. Intensive Care Med 2018;44 (9):1532--1535.
16. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 1982;126(5):788-791.
17. Chiumello D, Consonni D, Coppola S, Froio S, Crimella F, Colombo A. The occlusion tests and end-expiratory esophageal pressure: measurements and comparison in controlled and assisted ventilation. Ann Intensive Care 2016;6(1):13.
18. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. Intensive Care Med 2006;32(1):34-47.

19. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med 2009;37(10):2740-2745.
20. de Haro C, Magrans R, López-Aguilar J, Montanyà J, Lena E, Subirà C, et al; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Effects of sedatives and opioids on trigger and cycling asynchronies throughout mechanical ventilation: an observational study in a large data set from critically ill patients. Crit Care 2019;23(1):245.
21. Nava S, Bruschi C, Fracchia C, Braschi A, Rubini F. Patient-ventilator interaction and inspiratory effort during pressure support ventilation in patients with different pathologies. Eur Respir J 1997;10(1):177-183.
22. Ciumas C, Rheims S, Ryvlin P. fMRI studies evaluating central respiratory control in humans. Front Neural Circuits 2022;16:982963.
23. Colombo D, Cammarota G, Alemani M, Carenzo L, Barra FL, Vaschetto R, et al. Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. Crit Care Med 2011;39 (11):2452-2457.
24. Ramirez II, Arellano DH, Adasme RS, Landeros JM, Salinas FA, Vargas AG, et al. Ability of ICU health care professionals to identify patient-ventilator asynchrony using waveform analysis. Respir Care 2017;62(2):144-149.
25. Blanch L, Sales B, Montanya J, Lucangelo U, Garcia-Esquirol O, Villagra A, et al. Validation of the Better Care system to detect ineffective efforts during expiration in mechanically ventilated patients: a pilot study. Intensive Care Med 2012;38(5):772-780.
26. Phan TS, Costa R, Haddad WM, Mullis JC, Price LT, Cason AD, et al. Validation of an automated system for detecting ineffective triggering asynchronies during mechanical ventilation: a retrospective study. J Clin Monit Comput 2020;34(6):1233-1237.
27. Dres M, Rittayamai N, Brochard L. Monitoring patient-ventilator asynchrony. Curr Opin Crit Care 2016;22(3):246-253.
28. Dzierba AL, Khalil AM, Derry KL, Madahar P, Beitler JR. Discordance between respiratory drive and sedation depth in critically ill patients receiving mechanical ventilation. Crit Care Med 2021;49 (12):2090-2101.
29. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, et al. Mechanical ventilation–induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. Chest 2013;143(4):927-938.
30. Dianti J, Bertoni M, Goligher EC. Monitoring patient-ventilator interaction by an end-expiratory occlusion maneuver. Intensive Care Med 2020;46(12):2338-2341.
31. Kyo M, Shimatani T, Hosokawa K, Taito S, Kataoka Y, Ohshimo S, Shime N. Patient-ventilator asynchrony, impact on clinical outcomes and effectiveness of interventions: a systematic review and meta-analysis. J Intensive Care 2021;9(1):50.