Original Contribution

Interventions affecting blood pressure variability and outcomes after intubating patients with spontaneous intracranial hemorrhage

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ABSTRACT

Introduction: Spontaneous intracranial hemorrhage (sICH) that increases intracranial pressure (ICP) is a life-threatening emergency often requiring intubation in Emergency Departments (ED). A previous study of intubated ED patients found that providing ≥5 interventions after initiating mechanical ventilation (pMVI) reduced mortality rate. We hypothesized that pMVIs would lower blood pressure variability (BPV) in patients with sICH and thus improve survival rates and neurologic outcomes.

Method: We performed a retrospective study of adults, who were transferred to a quaternary medical center between 01/01/2011 and 09/30/2015 for sICH, received an extraventricular drain during hospitalization. They were identified by International Classification of Diseases, version 9 (430.XX, 431.XX), and procedure code 02.21. Outcomes were BPV indices, death, and being discharged home.

Results: We analyzed records from 147 intubated patients transferred from 40 EDs. Forty-one percent of patients received ≥5 pMVIs and was associated with lower median successive variation in systolic blood pressure (BP_{SV}) (31,[IQR 18–45) compared with those receiving 4 or less pMVIs (38[IQR 16–70]], $p = 0.040$). Three pMVIs, appropriate tidal volume, sedative infusion, and capnography were significantly associated with lower BPV. In addition to clinical factors, BP_{SV} (OR 26; 95% CI 1.2, >100) and chest radiography (OR 0.3; 95% CI 0.09, 0.9) were associated with mortality rate. Use of quantitative capnography (OR 8.3; 95%CI, 4.7, 8.8) was associated with increased likelihood of being discharged home.

Conclusions: In addition to disease severity, individual pMVIs were significantly associated with BPV and patient outcomes. Emergency physicians should perform pMVIs more frequently to prevent BPV and improve patients' outcomes.

1. Introduction

Spontaneous intracranial hemorrhage that elevates intracranial pressure (ICP) is a neurologic emergency with a high mortality rate (35–52%) [1]. Patients with that combination usually require invasive mechanical ventilation, which Zafar and colleagues found to be an independent risk factor for mortality [2]. Since cerebral perfusion pressure (CPP) is dependent on mean arterial pressure (MAP) [3], patients with

spontaneous intracranial hemorrhage are susceptible to secondary injuries, such as hypocapnia [4] and blood pressure variability, which is associated with early neurologic deterioration [5,6] and an increased risk of death [6-8]. Blood pressure variability is defined as the average of absolute differences between consecutive blood pressure measurements (successive variation [BP_{SV}]), variation of blood pressure during a period of time (standard deviation [BP_{SD}]), or coefficient of variation [BP_{CV}]) [7].

Emergency physicians (EPs) frequently intubate critically ill patients in the ED; however, they usually do not have significant training in mechanical ventilation [9], increasing the risk of its inadequate management [10]. As a result, extended length of stay (LOS) in the ED has been associated with worse outcomes for intubated trauma [11] and non-trauma patients [12]. While there is scant information about what constitutes good clinical practice for management following mechanical ventilation in the ED, EPs' proper interventions for mechanically

ventilated patients were associated with improved patients' outcomes. Fuller and associates showed that introduction of a lung-protective protocol for patients with acute respiratory distress syndrome (ARDS) improved outcomes [13]. Bhat and colleagues [14] found that performing five of the following seven post-mechanical ventilation interventions improved the outcomes of patients destined for a medical intensive care unit (ICU): 1) having appropriate tidal volume, 2) confirming proper endotracheal tube position by chest X-ray, 3) checking arterial blood gas (ABG) values, 4) inserting an orogastric or a nasogastric tube for gastric decompression, 5) inserting a urethral Foley catheter, 6) monitoring patients via quantitative capnography, and 7) administering sedatives early.

The purpose of our study was to elucidate whether providing 5 or more post mechanical ventilation interventions would affect blood pressure variability during the ED stays of patients with spontaneous intracranial hemorrhage and elevated ICP, prior to transferring to a quaternary academic center. Consequently, we also investigated whether providing any individual post mechanical ventilation intervention would also be associated with blood pressure variability and outcomes in these critically ill patients.

2. Methods

2.1. Study settings

We retrospectively reviewed the charts of adults who experienced spontaneous intracranial hemorrhage, were transferred to an academic quaternary center (UMMC), and underwent extraventricular drain (EVD) placement to temporarily relieve intracranial hypertension, during hospitalization. Patients who were transferred from any referring EDs between 01/01/2011 and 09/30/2015 were included. Patients were identified by International Classification of Diseases, version 9 (ICD-9), code 430.XX or 431.XX [15,16] and procedure code 02.21 [16]. The study was approved by the institutional review board at the medical center with which the corresponding author is affiliated.

We excluded patients who were not transferred directly from referring EDs as well as those who were not accompanied by complete ED records. Because of our institution's clinical policy, we also excluded patients who presented initially to our academic ED: after patients are admitted to an inpatient team, such as the neurology critical care unit (NCCU), they are not actively managed by ED providers, unless their conditions deteriorate. Therefore, the management of admitted and ED-boarding patients does not accurately reflect care by ED providers.

2.2. Data collection and management

The principal investigator of the study (QKT) trained other research team members (GT, AU, JR, KP, TN, MCP, and HA) in data extraction. The team members were blinded to the study's hypothesis. Data were extracted to a standardized Microsoft Access database (Microsoft Corp, WA). To minimize bias, each investigator independently extracted separate variables. Up to 50% of the data were checked by the principal investigator to maintain an inter-rater agreement of at least 90%. The group met every 3 months to discuss issues regarding data interpretation, data extractions, and data adjudication until data collection was complete.

2.2.1. Independent variables
We obtained demographic and clinical data from three sources: referring ED records, transportation teams' documentation, and ICU records. Demographic data included date and time of ED triage and departure from the referring ED, age, gender, weight, and height. Clinical data included vital signs and Glasgow Coma Scale (GCS) scores at triage and ED departure, the presence of seizure prior to or during the ED stay, ED tidal volume, and the results of arterial blood gas (ABG) analysis.

We used the seven interventions delineated by Bhat et al. [14]: 1) appropriate tidal volume, defined as 6 to 8 ml per kilogram (kg) of ideal body weight; 2) documentation of confirmation of proper ETT positioning with chest X-ray, 3) insertion of an orogastric or a nasogastric tube for gastric decompression, 4) insertion of a urethral Foley catheter, 5) ABG analysis, 6) initiation of continuous sedative infusion, and 7) use of quantitative capnography. We recorded the use of any post mechanical ventilation intervention documented in any of the data sources as when it was performed, not when it was ordered by an emergency care provider.

2.3. Blood pressure variability

Blood pressure variability has been shown to be associated with poor outcome in patients with spontaneous intracranial hemorrhage [6-8,17]. Since ED staff members do not record blood pressure measurements regularly or hourly, we extracted four of those measurements at clinically meaningful points: at ED triage (BP_{Triage}) and at ED departure (BP_{depart}) and then the highest one (BP_{high}) and the lowest one (BP_{low}) during the ED stay. The BP_{high} and BP_{low} values were not the same as the BP_{triage} and BP_{depart} values. If the BP at triage or departure happened to be the highest or lowest value, then the next higher or lower value during the ED stay was recorded.

The magnitude of systolic blood pressure during the ED stay ($MAC_{depart-triage}$) was calculated as previously described [5,8]: $\sqrt{(BP_{depart} - BP_{triage})^2}$. The magnitude of absolute change between the high and low systolic blood pressures ($MAC_{High-Low}$) was calculated as $MAC_{High-Low} = (SBP_{High} - SBP_{Low})$. The standard deviation of BP (BP_{SD}) was calculated [18,19] as $\sqrt{\left(\frac{1}{n-1}\right) \int_{(i=1)}^{(n-1)} (BP_i - BP_{mean})^2}$. The coefficient of variation of BP (BP_{CV}) was calculated as $\left(\frac{SD}{mean}\right) X100$ [5,17,20]. Successive variations in blood pressure (BP_{SV}) were calculated [17,19,20] with the following equation: $BP_{SV} = \sqrt{\left(\frac{1}{n-1}\right) \int_{i=1}^{(n-1)} (SBP_{i+1} - SBP_i)^2}$.

2.4. Outcome

Our primary outcome was the difference in blood pressure variability indices among patients receiving four or fewer post mechanical ventilation interventions versus those receiving five or more. The rationale for selecting this number of interventions was based on the study by Bhat and colleagues [14]. Secondary outcomes were Glasgow Coma Scale on hospital day 5, which is associated with 90-day functional outcome [21], being discharged directly to home, and death during hospitalization. We also examined factors associated with these outcomes.

2.5. Data analysis

Descriptive analyses involving demographic and clinical data were used to describe characteristics of all patients requiring invasive mechanical ventilation and to compare patients receiving five or more post mechanical ventilation interventions with those receiving four or fewer of them. Continuous data were first tested for normality using the Shapiro-Wilk test and were then expressed as mean (standard deviation [SD]) or median with interquartile (IQR) ranges and analyzed by the student t-test or the Mann Whitney U test when appropriate. A chi-squared test with Yates correction was used to compare categorical data.

Backward stepwise multiple linear regression was used to assess correlations between patients' characteristics, individual post mechanical ventilation interventions, and continuous outcomes. Prior to performing regression analyses, we logarithmically transformed nonparametric continuous data. We used multivariable logistic regression to assess associations between clinical data and two outcomes: in-hospital mortality and being discharged directly to home. All statistical

tests were performed with Sigma Plot version 13 (Systat Software, San Jose, CA, USA), and a *p*-value <0.05 was considered significant.

3. Results

During our study period, 378 patients met our ICD-9 criteria. For a variety of reasons (Fig. 1), 231 were excluded, leaving 147 mechanically ventilated patients with spontaneous intracranial hemorrhage who were transferred from approximately 40 EDs and underwent EVD placement during hospitalization at our quaternary medical center. We divided the patients into two groups: Group A comprised 87 patients who received four post mechanical ventilation interventions or fewer and Group B comprised 60 patients who received five or more post mechanical ventilation interventions (Table 1). The two groups' characteristics were similar except for two variables: Group A had a significantly higher median GCS score at triage (10 [IQR, 6–14] vs 7 [IQR, 4–9] [*p* = 0.049]) and a shorter duration of mechanical ventilation in the ED (79 [IQR, 52–125] vs 121 min [IQR, 82–155] [*p* < 0.001]) (Table 1).

The two groups had similar percentages of appropriate tidal volume and similar percentages of endotracheal tube confirmation by chest X-ray, gastric decompression, and Foley catheter insertion (Table 2A). Group B had significantly higher percentages of ABG analysis, continuous sedative infusion, and monitoring with quantitative capnography (Table 2A). Both groups also had similar patterns of induction medication or paralytics used for intubation (Table 2B). Similarly, ventilation modes and ventilator settings were also similar between 2 groups (Table 2B).

Backward stepwise multiple linear regression analysis showed that three clinical factors (age, systolic blood pressure, and GCS score at ED triage) were significantly associated with several indices of Blood Pressure Variability, i.e., BP_{SV}, BP_{SD}, and BP_{CV}. Having either one of three post mechanical ventilation interventions—appropriate tidal volume, continuous sedative infusion, and quantitative capnography—was associated with less blood pressure variability (Table 3). Appropriate tidal volume (6–8 ml/kg) was associated with less BP_{SV}, BP_{SD}, and BP_{CV}; continuous sedative infusion and quantitative capnography were associated with less BP_{SD} and BP_{CV}. Although there was no significant correlation between any individual post mechanical ventilation intervention with Glasgow Coma Scale on hospital day 5, younger age (coefficient 0.92, *p* = 0.008), higher triage GCS score (coefficient 1.14, *p* = 0.001) and lower $MAC_{Depart-Triage}$ (coefficient 0.99, *p* < 0.001) were associated with higher Glasgow Coma Scale on hospital day 5 (Table 3).

Multiple logistic regression analyses showed that age (odds ratio [OR] 1.9, 95% confidence interval (CI) 1.2,2.9) and GCS score at triage (OR 0.57, 95% CI 0.3, 0.9) were significantly associated with death during hospitalization. Higher BP_{SV} (OR 26, 95% CI 1.3, >100, *p* = 0.036) and $MAC_{Depart-Triage}$ (OR 1.02, 95% CI 1.003, 1.04) were associated with higher odd ratios for in-hospital mortality (Table 4). Similarly, the use of quantitative capnography (OR 8.3, 95% CI 4.7, 8.8) was associated with increased odds of being discharged home directly. In contrast, increased $MAC_{High-Low}$ (OR 0.92, 95% CI 0.88, 0.98) during the ED stay was associated with lower odds of being discharged home directly from the hospital.
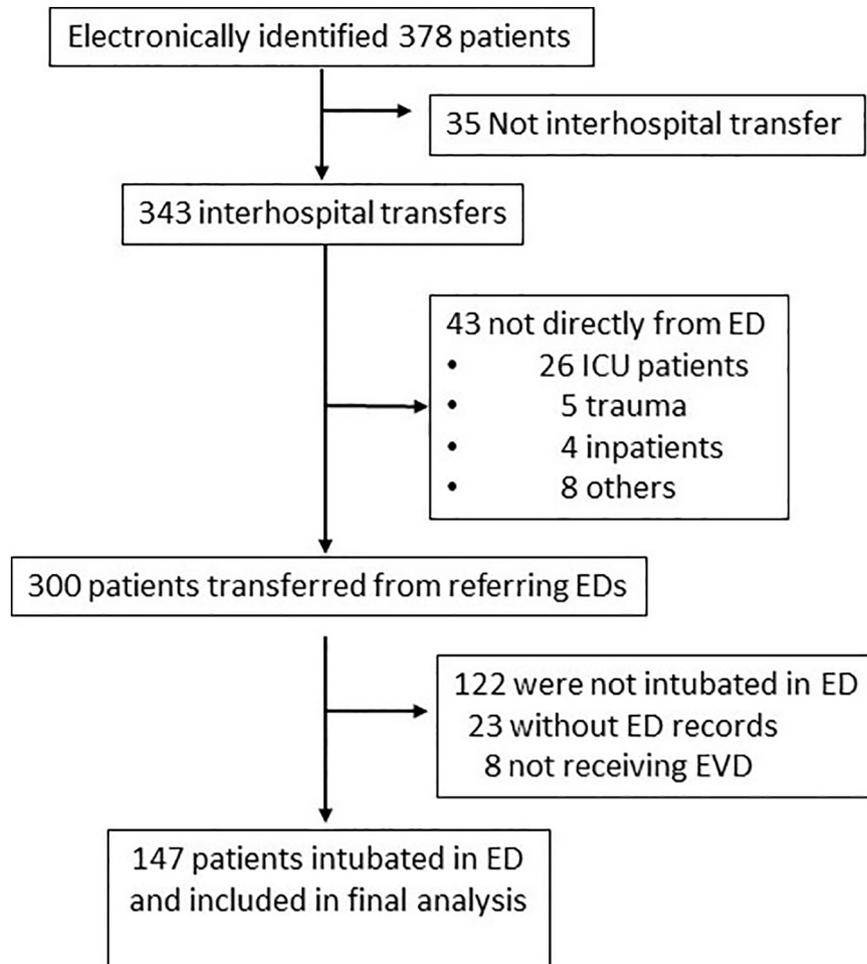

Fig. 1. Patient selection diagram.

Table 1
Characteristics of patients with spontaneous intracranial hemorrhage requiring intubation at referring EDs prior to transfer to a quaternary academic medical center.

	All MV patients (N = 147)	≤4 interventions (Group A) (N = 87)	≥5 interventions (Group B) (N = 60)	p-Value (A vs B)
Age (years), mean (SD)	58 (14)	60 (14)	56 (13)	0.07
Gender				
Female, N (%)	81 (55)	49 (56)	32 (53)	0.84
Male, N (%)	66 (45)	38 (44)	28 (47)	
Transport Type				
Ground, N (%)	95 (65)	58 (67)	37 (62)	0.66
Air, N (%)	52 (35)	29 (33)	23 (38)	
Type of hemorrhage				
IPH	63 (43)	52 (60)	32 (53)	0.77
SAH	84 (57)	35 (40)	28 (47)	
Seizure, N (%)				
No	125 (85)	71 (82)	54 (90)	0.24
Yes	22 (15)	16 (18)	6 (10)	
ESI, median [IQR]	2 [1–2]	2 [1–2]	1 [1–2]	0.45
Triage GCS, median [IQR]	9 [5–13]	10 [6–14]	7 [4–13]	0.049
Triage SBP (mm Hg), mean (SD)	184 (41)	183 (40)	185 (42)	0.74
Departure SBP, mean (SD)	147 (29)	147 (27)	148 (31)	0.77
Duration of MV in ED (min), median [IQR]	95 [60–145]	79 [52–125]	121 [82–155]	<0.001
ED LOS (min), median [IQR]	171 [129–213]	171 [121–209]	171 [140–217]	0.342
ICU First GCS, median [IQR]	7 [4–8]	7 [4–9]	6 [4–8]	0.64
Intracranial opening pressure (cm H_2O), mean (SD)	25 [15–30]	25 [15–30]	25 [17–30]	0.21
BP_{SV}	35 [21–50]	38 [25–55]	31 [18–45]	0.040
BP_{SD}	47 [32–63]	48 [30–62]	45 [33–65]	0.98
BP_{CV}	31 [20–41]	31 [20–40]	30 [21–43]	0.94
$MAC_{depart-triage}$	45 (34)	44 (32)	47 (38)	0.54
$MAC_{high-low}$	58 (38)	62 (36)	53 (41)	0.17
HD5 GCS, median [IQR]	10 [5–13]	10 [5–11]	10 [5–11]	0.49
Survivors' LOS (day), median [IQR]	27 [18–35]	25 [18–33]	27 [20–36]	0.26
Mortality, N (%)	49 (33)	31 (36)	18 (30)	0.59
Discharge home, N (%)	16 (11)	9 (10)	7 (12)	1

Abbreviations: BP_{SV}, successive variation in blood pressure; BP_{SD}, standard deviation of blood pressure; BP_{CV}, coefficient variation of blood pressure; cm, centimeter; ED, emergency department; ESI, Emergency Severity Index; GCS, Glasgow Coma Scale; HD5GCS, GCS score on hospital day 5; ICU, intensive care unit; IMV, invasive mechanical ventilation; IPH, intraparenchymal hemorrhage; IQR, interquartile range; LOS, length of stay; $MAC_{depart-triage}$, magnitude of absolute change between triage and departure blood pressures; min, minute; MV, mechanical ventilation; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SD, standard deviation.

4. Discussion

In this study of patients with spontaneous intracranial hemorrhage and elevated ICP being intubated in an ED, those who received five or more post mechanical ventilation interventions had less successive variation in blood pressure (BP_{SV}), which was associated with a lower odds ratio of in-hospital mortality. In addition to clinical factors such as systolic blood pressure at triage and at departure, providing any of the three post mechanical ventilation interventions was associated with less blood pressure variability. One post mechanical ventilation intervention, confirming endotracheal tube placement with chest X-ray, was associated with a significantly lower likelihood of death during hospitalization. Another post mechanical ventilation intervention,

Table 2A
Comparison of frequencies of post-intubation interventions between groups of mechanically ventilated patients.

Intervention, N (%)[a]	All patients	≤4 interventions (Group A)	≥5 interventions (Group B)	p-Value
Appropriate tidal volume	104 (71)	51 (35)	53 (36)	0.9
Chest X-ray	117 (80)	63 (43)	54 (37)	0.34
Gastric decompression	113 (77)	57 (39)	56 (38)	1.0
Urethral Foley catheter	129 (88)	71 (48)	58 (40)	0.16
ABG analysis	61 (41)	22 (15)	39 (27)	0.02[b]
Continuous sedative infusion	69 (47)	24 (16)	45 (31)	<0.01[c]
Quantitative capnography	18 (12)	4 (3)	14 (10)	0.03[d]

[a] Percentages were calculated based on total number of patients (N = 147).
[b] OR 0.5 (95% CI 0.27, 0.87).
[c] OR 7.9 (95% CI 3.7, 6.7).
[d] OR 0.27 (95% CI 0.08, 0.83).

monitoring patients with quantitative capnography, was associated with an increased odds ratio of discharge directly to home.

Our finding that increased BP_{SV} and $MAC_{Depart-Triage}$ during ED stay were associated with a higher odds ratio of in-hospital mortality is supported by previous studies [6-8]. The mechanism by which blood pressure variability affects outcome in patients with spontaneous intracranial hemorrhage is still unknown. Manning and colleagues hypothesized that large fluctuations in systolic blood pressure could impair cerebral autoregulation [7]. Blood pressure variation might increase oncotic and hydrostatic pressure gradients in the perihematomal region, which would exacerbate cerebral edema [7,22]. Therefore, maintaining consistent blood pressure while minimizing blood pressure variability is important for enhancing patient outcome [7,22]. Performing a few post mechanical ventilation interventions was crucial because they were associated with decreased blood pressure variability, and even a short period of blood pressure variability during ED stay adversely affects the mortality rate, according to our data. Therefore, it is good clinical practice for emergency physicians to direct the ED staff to perform all appropriate post mechanical ventilation interventions on patients with spontaneous intracranial hemorrhage and increased ICP during ED stay to avoid early blood pressure variability and thus potentially improve outcomes.

Our finding that confirming endotracheal tube placement with chest X-ray was associated with lower mortality is consistent with findings reported by Bhat et al. [14], who showed that ED patients, destined for medical intensive care unit and underwent chest-X-ray for endotracheal tube placement confirmation, had a reduced risk of death (OR 0.10, 95% CI 0.01, 0.98). However, Bhat's study did not show that the use of quantitative capnography was associated with outcome. In contrast, patients in our study who were monitored with quantitative capnography had a significantly higher likelihood of being discharged home. This observation suggests that physicians who monitor patients

Table 2B
Intubation medication and mechanical ventilator settings in patients with intracranial hemorrhage and requiring mechanical ventilation in ED.

	All Patients (N = 147)	≤4 Interventions (Group A) (N = 87)	≥5 Interventions (Group B) (N = 60)	p-value (A vs B)
Induction medication, N (%)				
Etomidate	92 (63)	52 (60)	40 (67)	0.49
Benzodiazepines	32 (22)	18 (20)	14 (23)	0.86
None	23 (15)	17 (20)	6 (10)	0.18
Paralytic Medication, N (%)				
Succinylcholine	65 (44)	36 (41)	29 (48)	0.51
Rocuronium	55 (37)	32 (37)	23 (38)	0.99
Vecuronium	4 (3)	2 (2)	2 (4)	0.99
None	23 (16)	17 (20)	6 (10)	0.16
Ventilator mode, N (%)				
PRVC	74 (50)	39 (45)	35 (58)	0.15
VC	61 (42)	41 (47)	20 (33)	0.13
Other[b]	12 (8)	7 (8)	5 (8)	0.89
FiO2, mean, SD	0.5 (0.2)	0.49 (16)	0.47 (14)	0.37
Respiratory rate, breaths per minute, mean (SD)	16 (3)	16 (3)	16 (2)	0.57
Tidal volume (ml)[a], mean (SD)	450 (57)	454 (58)	452 (55)	0.79
PEEP, cm H_2O, mean (SD)	6 (2)	5.7 (2)	5.9 (2)	0.31
Peak airway pressure, cm H_2O, mean (SD)	21.4 (6)	22 (6)	21 (7)	0.48

Cm, centimeter; FiO$_2$, fraction of inspired oxygen; H_2O, water; ml, milliliter; PEEP, Positive End Expiratory Pressure; PRVC, Pressure-regulated, volume-control; SD Standard Deviation; VC, volume control.

[a] Tidal volume (milliliter) per kilogram of ideal body weight was reported in Table 2A.
[b] Other modes of ventilator settings (2 [1.3%] Continuous Mandatory Ventilation [CMV], 4 (2.7%) synchronized intermittent mechanical ventilation [SIMV], 6 Pressure Control [PC]).

with capnography receive frequent and early information that enables them to adjust ventilator settings to prevent hypocapnia and hypercapnia. Hypocapnia is associated with cerebral vasoconstriction and consequently poor outcome in these high-risk patients [4,23] and duration of hypocapnia has been associated with poor outcome among patients with subarachnoid hemorrhage [4].

To our knowledge, our study is the first to suggest factors that could be associated with blood pressure variability among patients who have spontaneous intracranial hemorrhage, elevated ICP and requiring invasive mechanical ventilation. In addition to patients' disease severity, three post mechanical ventilation interventions, maintaining appropriate tidal volume, infusing sedative medications, and the use of capnography, were also associated with blood pressure variability. On the other hand, reverse causality between blood pressure variability and those 3 post mechanical ventilation interventions cannot be

excluded. It is possible that emergency physicians initiate more interventions when they recognize that patients have blood pressure variability; for example, they might start sedative infusions or adjust the ventilator settings to resolve patient–ventilator dyssynchrony. Therefore, it is recommended that physicians initiate early and deep sedation of patients with spontaneous intracranial hemorrhage in the hyperacute phase to avoid blood pressure variability. Light sedation is associated with increased catecholamine production [24], resulting in higher blood pressure variability.

5. Limitations

Our study has several limitations in addition to its retrospective nature. We did not have access to Computer Tomography (CT) results from the referring EDs, so we could not assess hematoma volume growth although previous studies suggested that components of blood pressure variability are not associated with increases in hematoma volume [7,17]. Additionally, for outcome, we did not calculate the modified Rankin Scale retrospectively because that calculation is unreliable [25]. We did not use hospital length of stay as an outcome because of it was not used in previous studies of blood pressure variability [6-8]. Furthermore, we calculated blood pressure variability from four readings per patient, during their short ED stay—fewer than a previous study, which collected five blood pressure measurements during the

Table 3
Backward stepwise linear regressions to measure associations between patients' clinical characteristics, individual post-mechanical ventilation interventions, indices of blood pressure variability, and Glasgow Coma Scale Score on Hospital Day 5 (HD5GCS).

Outcome (Adj. R-square)	Variables	Coefficient[a]	p-Value
BP$_{SV}$ (0.12)	Appropriate tidal volume	0.61	0.008
	Triage SBP	1.2	<0.001
	Departure SBP	0.91	0.047
BP$_{SD}$ (0.27)	Appropriate tidal volume	0.81	0.034
	Continuous sedative infusion	0.80	0.018
	Quantitative capnography	0.76	0.043
	Triage SBP	1.18	<0.001
BP$_{CV}$ (0.25)	Appropriate tidal volume	0.82	0.038
	Continuous sedative infusion	0.80	0.019
	Quantitative capnography	0.77	0.038
	Triage SBP	1.2	<0.001
MAC$_{Depart-Triage}$ (0.42)	Triage GCS	−4.1	0.038
MAC$_{High-Low}$ (0.07)	Triage SBP	6.7	0.002
HD5GCS (0.2)	Age	0.92	0.03
	Triage GCS	1.14	0.001
	MAC$_{Depart-Triage}$	0.99	<0.001

Abbreviations: Adj., adjusted; BP$_{SV}$ successive variation of blood pressure; BP$_{SD}$, standard deviation of blood pressure; BP$_{CV}$, coefficient variation of blood pressure; GCS, Glasgow Coma Scale; HD5GCS, GCS score on hospital day 5; MAC$_{Depart-Triage}$, magnitude of absolute change between departure and triage systolic blood pressure; MAC$_{High-Low}$, magnitude of absolute change between high and low systolic blood pressure readings during ED stay; SBP, systolic blood pressure.

[a] Prior to analysis, values of BP$_{SV}$; BP$_{SD}$, BP$_{CV}$, HD5GCS were logarithmically-transformed; the coefficients were re-transformed for reporting.

Table 4
Multivariable logistic regressions assessing association between patients' characteristics, post-mechanical ventilation interventions and the likelihood of in-hospital mortality or being discharged home.

Outcome	Variables	ORs	95% CI	p-value
Mortality				
	Age	1.9	1.2, 2.9	0.003
	Triage GCS	0.57	0.3, 0.9	0.038
	Chest X-ray	0.30	0.09, 0.9	0.042
	BP$_{SV}$	26	1.3, >100	0.036
	MAC$_{Depart-Triage}$	1.02	1.003, 1.04	0.021
Discharging home				
	MAC$_{High-Low}$	0.92	0.88, 0.98	0.003
	Quantitative capnography	8.3	4.7, 8.8	0.002

Abbreviations: BP$_{SV}$, successive variation in blood pressure; CI, confidence interval; MAC$_{depart-triage}$, magnitude of absolute change between triage and departure blood pressures; MAC$_{High-Low}$, magnitude of absolute change between high and low systolic blood pressures during ED stay; OR, odds ratio; XR, radiograph.

hyperacute phase of up to 6 h from symptoms onset [8] and extension of the observation period might have resulted in a different blood pressure variability calculation among these patients. Finally, we did not assess the effect of blood-pressure-lowering medications by EPs on our patients during their ED stays because nicardipine infusion lowers BP in a more controlled fashion than other hypertensive medications [26].

6. Conclusions

While patients' disease severity might correlate with blood pressure variability and outcomes, the use of three post mechanical ventilation interventions in the ED showed correlation with blood pressure variability among intubated patients with spontaneous intracranial hemorrhage. To reduce blood pressure variability and maximize outcomes, emergency physicians should maintain appropriate tidal volume, initiate continuous infusion of a sedative medication, and confirm proper endotracheal tube positioning via chest radiography, and use quantitative capnography to monitor patients' respiratory status.

Presentation

The results of this study were presented in part at the 2017 American College of Emergency Physicians (ACEP), Washington DC October 2017.

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Authors' contributions

GT, AU, JS participated in study concept and design; data acquisition, analysis, and interpretation; drafting of the manuscript; and critical revision of the manuscript.

WC participated in study concept and design, drafting of the manuscript, and critical revision of the manuscript.

RJ, KP, TN, DG, and HAR participated in data acquisition and provided critical revision of the manuscript.

QKT participated in study concept and design; data acquisition, analysis, and interpretation; drafting of the manuscript; and critical revision of the manuscript.

Conflict of interest disclosure

The authors have no conflict of interest to declare. JMH has received funding from Pfizer, Inc., for consulting related to sickle cell disease.

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Appendix 1. Multiple logistic regressions between patients' characteristics and outcomes (in-hospital mortality, being discharged home)

Outcome	Variables	OR	95% CI	p-Value
In-hospital mortality	Age	1.9	1.2, 2.9	0.003
	Gender	1.5	0.6, 3.7	0.44
	Triage GCS	0.57	0.3, 0.9	0.038
	Type of hemorrhage	0.79	0.32, 1.9	0.62
	ESI	1.2	0.6, 2.1	0.64
	Transport type	1.45	0.46, 4.8	0.51
	Seizure	1.03	0.3, 4.3	0.96

(continued)

Outcome	Variables	OR	95% CI	p-Value
	Length of MV in ED	0.99	0.99, 1.005	0.28
	ED LOS	1.05	0.67, 1.6	0.66
	BP_{SV}	26	1.4, >100	0.036
	BP_{SD}	0.58	<0.01, >100	0.25
	BP_{CV}	2.5	<0.01, >100	0.31
	$MAC_{depart-triage}$	1.02	1.003, 1.04	0.021
	$MAC_{high-low}$	1.0	0.89, 1.02	0.64
	Appropriate tidal volume	1.3	0.5, 4.4	0.54
	Chest X-ray	0.30	0.09, 0.95	0.042
	Gastric decompression	0.91	0.36, 3.0	0.93
	Urethral Foley catheter	0.35	0.09,1.3	0.13
	Checking ABG	1.3	0.46, 3.6	0.63
	Continuous sedative infusion	1.3	0.5, 3.1	0.59
	Quantitative capnography	0.51	0.1, 2.1	0.37
Discharging home	Age	0.62	0.9, 4.5	0.21
	Gender	0.1	0.01, 1.4	0.9
	Triage GCS	2.0	0.89, 4.5	0.09
	Type of hemorrhage	0.6	0.07, 4.6	0.61
	ESI	3.1	0.6, 15	0.16
	Transport type	2.7	0.24, 30	0.41
	Seizure	2.9	0.2, 41	0.42
	Length of MV in ED	0.61	0.25, 1.5	0.29
	ED LOS	0.72	0.3, 1.6	0.40
	BP_{SV}	6.1	0.03, >100	0.50
	BP_{SD}	1.9	<0.1, >100	0.63
	BP_{CV}	0.1	<0.1, >100	0.77
	$MAC_{depart-triage}$	0.97	0.94, 1.1	0.09
	$MAC_{high-low}$	0.92	0.88, 0.98	0.004
	Appropriate tidal volume	0.74	0.2, 3.1	0.38
	Chest X-ray	1.3	0.18, 8.9	0.79
	Gastric decompression	3.8	0.3, 47	0.29
	Urethral Foley catheter	15	0.01, >100	0.99
	Checking ABG	0.71	0.2, 3.1	0.59
	Continuous sedative infusion	0.66	0.2, 2.5	0.37
	Quantitative capnography	8.3	4.7, >100	0.002

Abbreviations: ABG, arterial blood gas; BP_{SV}, successive variation in blood pressure; BP_{SD}, standard deviation of blood pressure; BP_{CV}, coefficient variation of blood pressure; ED, emergency department; GCS, Glasgow Coma Scale; ETT, endotracheal tube; $MAC_{depart-triage}$, magnitude of absolute change between triage and departure blood pressure; SD, standard deviation; BP_{SV}, SV successive variation.

References

[1] Testai FD, Aiyagari V. Acute hemorrhagic stroke pathophysiology and medical interventions: blood pressure control, management of anticoagulant-associated brain hemorrhage and general management principles. Neurol Clin 2008;26(4):963–85. https://doi.org/10.1016/j.ncl.2008.06.001.

[2] Zafar SF, Postma EN, Biswal S, Fleuren L, Boyle EJ, Bechek S, et al. Electronic health data predict outcomes after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2018;28(2):184–93. https://doi.org/10.1007/s12028-017-0466-8.

[3] J-PAH Jantzen. Prevention and treatment of intracranial hypertension. Best Pract Res Clin Anaesthesiol 2007;21(4):517–38. https://doi.org/10.1016/j.bpa.2007.09.001.

[4] Solaiman O, Singh JM. Hypocapnia in aneurysmal subarachnoid hemorrhage: incidence and association with poor clinical outcomes. J Neurosurg Anesthesiol 2013;25(3):254–61. https://doi.org/10.1097/ANA.0b013e3182806465.

[5] Duan Z, Tao L, Tang T, Fu C, Liu J, Chen B, et al. Effect of blood pressure variability on early neurological deterioration in single small subcortical infarction with parental arterial disease. Neurol Sci 2017;8:22–7. https://doi.org/10.1016/j.ensci.2017.06.006.

[6] Tanaka E, Koga M, Kobayashi J, et al. Blood pressure variability on antihypertensive therapy in acute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke 2014;45(8):2275–9. https://doi.org/10.1161/STROKEAHA.114.005420.

[7] Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol 2014;13(4):364–73.

[8] Chung P-W, Kim J-T, Sanossian N, Starkmann S, Hamilton S, Gornbein J, et al. Association between hyperacute stage blood pressure variability and outcome in patients with spontaneous intracerebral hemorrhage. Stroke 2018;49(2):348–54. https://doi.org/10.1161/STROKEAHA.117.017701.

[9] Wilcox SR, Strout TD, Schneider JI, Mitchell PM, Smith J, Lutfy-Clayton L, et al. Academic emergency medicine physicians' knowledge of mechanical ventilation. West J Emerg Med 2016;17(3):271–9. https://doi.org/10.5811/westjem.2016.2.29517.

[10] Wilcox SR, Richards JB, Fisher DF, Sankoff J, Seigel TA. Initial mechanical ventilator settings and lung protective ventilation in the ED. Am J Emerg Med 2016;34(8):1446–51. https://doi.org/10.1016/j.ajem.2016.04.027.

[11] Carr BG, Kaye AJ, Wiebe DJ, Gracias VH, Schwab CW, Reilly PM. Emergency department length of stay: a major risk factor for pneumonia in intubated blunt trauma patients. J Trauma 2007;63(1):9–12.

[12] Angotti LB, Richards JB, Fisher DF, Sankoff JD, Seigel TA, Al Ashry HS, et al. Duration of mechanical ventilation in the emergency department. West J Emerg Med 2017;18 (5):972–9. https://doi.org/10.5811/westjem.2017.5.34099.

[13] Fuller BM, Ferguson IT, Mohr NM, Drewry AM, Palmer C, Wessman BT, et al. A quasi-experimental, before-after trial examining the impact of an emergency department mechanical ventilator protocol on clinical outcomes and lung-protective ventilation in acute respiratory distress syndrome. Crit Care Med 2017;45(4):645–52. https://doi.org/10.1097/CCM.0000000000002268.

[14] Bhat R, Goyal M, Graf S, Bhoosan A, Teferra E, Dubin J, et al. Impact of post-intubation interventions on mortality in patients boarding in the emergency department. West J Emerg Med 2014;15(6):708–11. https://doi.org/10.5811/westjem.2014.7.22292.

[15] Lai PMR, Dasenbrock H, Lin N, Du R. The impact of insurance status on the outcomes after aneurysmal subarachnoid hemorrhage. PLoS One 2013;8(10):e78047. https://doi.org/10.1371/journal.pone.0078047.

[16] Fargen KM, Neal D, Rahman M, Hoh BL. The prevalence of patient safety indicators and hospital-acquired conditions in patients with ruptured cerebral aneurysms: establishing standard performance measures using the Nationwide Inpatient Sample database. J Neurosurg 2013;119(6):1633–40. https://doi.org/10.3171/2013.7.jns13595.

[17] Jeon J, Kim C, Kim S-E. Blood pressure variability and outcome in patients with acute nonlobar intracerebral hemorrhage following intensive antihypertensive treatment. Chin Med J 2018;131(6):657–64. https://doi.org/10.4103/0366-6999.226886.

[18] Bennett AE, Wilder MJ, McNally JS, et al. Increased blood pressure variability after endovascular thrombectomy for acute stroke is associated with worse clinical outcome. J Neurointerv Surg 2018 Jan 19. https://doi.org/10.1136/neurintsurg-2017-013473 [Epub ahead of print].

[19] Endo K, Kario K, Koga M, Nakagawara J, Shiokawa Y, Yamagami H, et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA registry. Stroke 2013;44(3):816–8. https://doi.org/10.1161/STROKEAHA.112.681007.

[20] de Havenon A, Bennett A, Stoddard GJ, Smith G, Chung L, O'Donnell S, et al. Determinants of the impact of blood pressure variability on neurological outcome after acute ischaemic stroke. Stroke Vasc Neurol 2017;2(1):1–6. https://doi.org/10.1136/svn-2016-000057.

[21] Maas MB, Francis BA, Sangha RS, Lizza BD, Liotta EM, Naidech AM. Refining prognosis for intracerebral hemorrhage by early reassessment. Cerebrovasc Dis 2017;43 (3–4):110–6. https://doi.org/10.1159/000452679.

[22] Sykora M, Diedler J, Rupp A, Turcani P, Rocco A, Steiner T. Impaired baroreflex sensitivity predicts outcome of acute intracerebral hemorrhage. Crit Care Med 2008;36 (11):3074–9. https://doi.org/10.1097/CCM.0b013e31818b306d.

[23] Williamson CA, Sheehan KM, Tipirneni R, Roark CD, Pandy AS, Thompson BG, et al. The association between spontaneous hyperventilation, delayed cerebral ischemia, and poor neurological outcome in patients with subarachnoid hemorrhage. Neurocrit Care 2015;23(3):330–8. https://doi.org/10.1007/s12028-015-0138-5.

[24] Kress JP, Vinayak AG, Levitt J, Schweickert WD, Gehlbach BK, Zimmerman F, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. Crit Care Med 2007;35(2):365–71. https://doi.org/10.1097/01.CCM.0000254334.46406.B3.

[25] Quinn TJ, Ray G, Atula S, Walters MR, Dawson J, Lees KR. Deriving modified Rankin scores from medical case-records. Stroke 2008;39(12):3421–3. https://doi.org/10.1161/STROKEAHA.108.519306.

[26] Peacock WF, Varon J, Baumann BM, Borczuk P, Cannon CM, Chandra A, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. Crit Care 2011;15(3):R157. https://doi.org/10.1186/cc10289.