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Original Article

Systolic blood pressure-adjusted stroke volume variation for intravascular volume assessment during norepinephrine infusion in elective craniotomy

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Abstract: Objective: Stroke volume variation (SVV) is widely used in goal-directed fluid therapy but is susceptible to interference from norepinephrine (NE), which biases intravascular volume assessment. This study aimed to characterize NE-induced SVV distortion and establish a corrected SVV parameter to improve volume evaluation during NE infusion. Methods: A total of 55 patients undergoing elective craniotomy were divided into a training cohort (n = 35) and a validation cohort (n = 20). Patients received an intraoperative dose of 0.5 g/kg mannitol or normal saline. NE was titrated during hypervolemic and hypovolemic phases differentiated by central venous pressure and urine output. Hemodynamic variables, blood gas parameters and postoperative complications were compared. Multivariate linear regression analysis using SBP, CI, SV, and NE dosage as independent variables was performed to derive the corrected SVV formula (BpSVV). Results: NE titration induced a stable negative linear correlation between SBP and SVV. The regression slopes of SBP-SVV curves were comparable between groups (P = 0.495), while the intercept significantly increased in the mannitol dehydration phase (P < 0.01). SBP predominantly determined SVV variation. A novel corrected parameter (BpSVV = SVV + 0.101 × ΔSBP) was established. The AUC values of BpSVV and raw SVV were 0.9167 and 0.9531 with favorable diagnostic efficiency. Logistic regression analysis showed that preoperative GCS score was significantly associated with poor postoperative neurological prognosis. Conclusions: Conventional SVV is markedly disturbed during titrated NE infusion. BpSVV could serve as a reliable alternative for intravascular volume assessment under such conditions.

Keywords: Goal directed fluid therapy, stroke volume variation, norepinephrine, cerebral anesthesia, mannitol

Introduction

Numerous studies have demonstrated that perioperative Goal-Directed Fluid Therapy (GDFT) under anesthesia can effectively alleviate tissue edema, reduce the risk of postoperative complications and improve prognosis [1, 2]. Among multiple monitoring methods for GDFT, stroke volume variation (SVV) obtained by the FloTrac/Vigileo system shows distinct clinical advantages [3-7]. This monitor connects directly to invasive arterial blood pressure equipment, sits remote from the surgical field, and provides continuous real-time updates. Its working principle involves continuously collecting beat-to-beat cardiac stroke volume (SV) values, calculating the fluctuation between maximum and minimum SV, and computing the ratio of this SV fluctuation to the mean SV. The widely accepted normal threshold for SVV is < 13% [8, 9]. Neurosurgical operations routinely employ SVV-guided restrictive fluid strategies combined with rapid mannitol infusion to reduce cerebral edema and facilitate surgical tissue dissection. Accumulated evidence has demonstrated that intraoperative SVV monitoring optimizes cerebral perfusion, alleviates blood-brain barrier damage, improves brain relaxation, and yields superior long-term neurological outcomes [6, 10, 11].

Nevertheless, SVV monitoring has inherent limitations. Vasopressors and intense surgical stimulation can substantially distort SVV via

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peripheral vasoconstriction [12-14]. So far, the characteristic disturbing laws of vasopressors on SVV and effective corrective strategies remain poorly researched. Prior studies have shown that norepinephrine (NE) infusion significantly lowers SVV but elevates cardiac index (CI), stroke volume index (SVI), and global end-diastolic volume index (GEDVI). Other reports have further demonstrated that NE impairs the predictive capacity of SVV for fluid responsiveness by increasing systemic vascular resistance (SVR), especially at high-dose (> 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) [12, 13, 15]. Clinically, SVV measurements are considered reliable only after vasopressors have been completely eliminated. However, NE is often indispensable during emergency or prolonged surgeries.

During neurosurgical procedure, transient hypotension frequently occurs following complete skull-flap removal. This hemodynamic fluctuation is attributed to the release of compressive force and the absence of nociceptive nerve fibers within the brain tissue. For the management of intraoperative hypotension, anesthesiologists routinely administer low-dose NE. Moreover, to obtain cerebral dehydration and optimize surgical visualization, surgeons often request 0.5-1.0 g/kg dose of mannitol rapid infusion. Numerous studies have demonstrated that this dosage improves cerebral perfusion while causing mild hypotension and dehydration [16-18]. Rapid mannitol infusion typically induces a marked reduction in blood pressure and a substantial increase in urine output, leading to two distinct intravascular volume states: hypervolemia before mannitol infusion and hypovolemia after mannitol infusion [19-22]. In neurosurgical procedures, surgical stimulation is minimal after the skull is removed, so its independent effect per se on SVV is negligible. Therefore, elective craniotomy could serve as an ideal clinical model for investigating the effects of NE infusion on SVV.

In other clinical emergency scenarios such as severe hemorrhagic shock, NE infusion is indispensable. Halting NE infusion for reliable SVV reference carries substantial clinical safety risks. However, blind reliance on NE-distorted SVV also leads to misjudgment of volume assessment, thereby impairing tissue perfusion. Therefore, it is imperative to investigate the specific interference patterns of NE on SVV, and develop the corresponding corrective strategy.

Materials and methods

Study design and ethics

This was a prospective, single-blind, self-controlled non-randomized observational study enrolling patients scheduled for elective surgery from December 2023 to August 2026. The trial protocol was approved by the Ethics Committee of Shenzhen People's Hospital (No. LL-KY-2023094-03. Approval date: September 11, 2023), and registered on the Chinese Clinical Trial Registry website (ChiCTR2300-078002. Registration date: November 27, 2023). The study adhered to the Good Clinical Practice guidelines and the ethical principles stated in the Declaration of Helsinki. Written informed consent was obtained from all subjects before enrollment. A total of 65 patients undergoing selective craniotomy at Shenzhen Peoples' Hospital were initially screened, and 55 patients were finally included. The Study Flow Diagram was presented in **Figure 1**.

Sample size calculation

Sample size was calculated by the formula: $n = 2(z_{\alpha}+z_{\beta})^{*}\sigma^{2}/d^{2}$, with $\alpha = 0.05$ and $\beta = 0.2$ (Sample Size Calculator: https://clincalc.com/stats/samplesize.aspx). SVV was designated as the primary endpoint, and parameters for sample size estimation were derived from our preliminary pilot data. In pilot trial, the mean SVV value of the control group was 9.57, while that of the mannitol group was 10.57. The pooled standard deviation of SVV was 0.93. With a 1:1 allocation ratio, the target sample size was calculated as $n \approx 14$ Considering the potential dropout rate and the interindividual variability in renal function affecting urine output, finally 55 patients were recruited.

Inclusion and exclusion criteria

Inclusion criteria: (1) Elective craniotomy for intracranial tumor resection without preoperative indications for emergency surgery; (2) Aged 18-75 years with ASA I-III; (3) Preoperative GCS score ≥ 10 capable of completing neurological and pain assessments; (4) BMI ranging from 18 to 32 kg/m^2, no anticipated

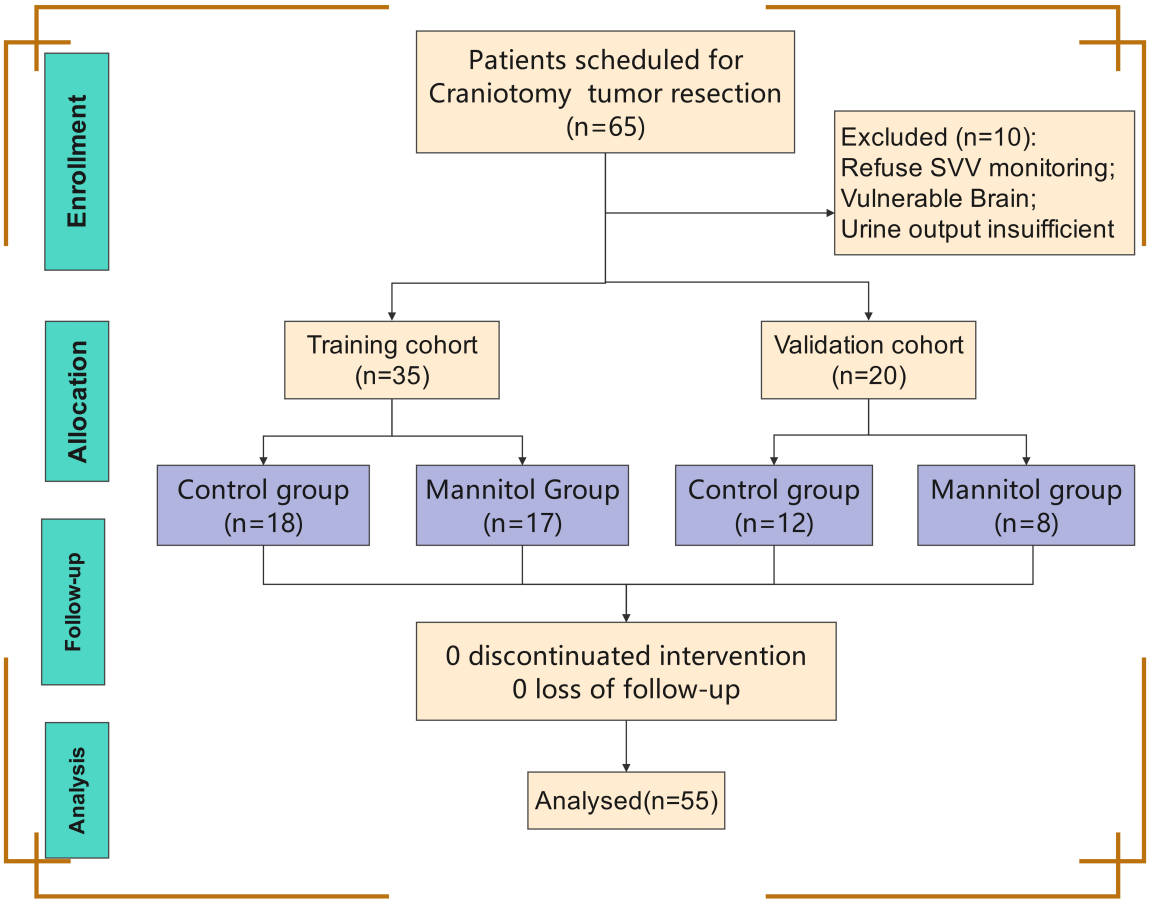


Figure 1. CONSORT flow diagram.

difficult airway; (5) Voluntarily signed informed consent.

Exclusion criteria: (1) Contraindications to SVV monitoring (significant arrhythmia or severe peripheral vascular disease); (2) Emergency surgery, brain herniation, tumor apoplexy, history of multiple prior craniotomies, multiple systemic metastases; (3) Preoperative GCS score < 10, severe cognitive dysfunction or aphasia, psychiatric disorders precluding cooperative assessment; (4) ASA physical status IV or higher, severe cardiac, hepatic, renal or pulmonary diseases, atrioventricular block, resting heart rate < 45 beats per minute; (5) Allergies to study anesthetics, local anesthetics or vasoactive agents; long-term use of opioids, glucocorticoids or clonidine; alcohol or drug dependence; (6) Pregnancy or lactation, coagulation disorders, poorly controlled severe diabetes mellitus; (7) Anticipated prolonged postoperative mechanical ventilation in ICU, full-length intraoperative neurophysiological monitoring, BMI < 18 or > 32 kg/m^2; (8) Refusal to provide informed consent, inability to complete follow-up.

Anesthesia

All participants received general anesthesia with endotracheal intubation. Anesthesia induction was conducted using propofol 2.0-2.5 mg/kg, sufentanil 0.5 μg/kg, and cisatracurium 0.2 mg/kg. Anesthesia maintenance was achieved with sevoflurane at 1-1.5 MAC, continuous remifentanil infusion at 0.1-0.15 μg·kg^{-1}·min^{-1}, and cis-atracurium 0.05 mg/kg per hour. After surgery, all patients received multimodal postoperative analgesia consisting of sufentanil 5 μg, flurbiprofen axetil 50 mg, and palonosetron 0.075 mg. Then right internal jugular vein catheterization was performed for central venous pressure (CVP) monitoring, and radial or dorsalis pedis artery cath-

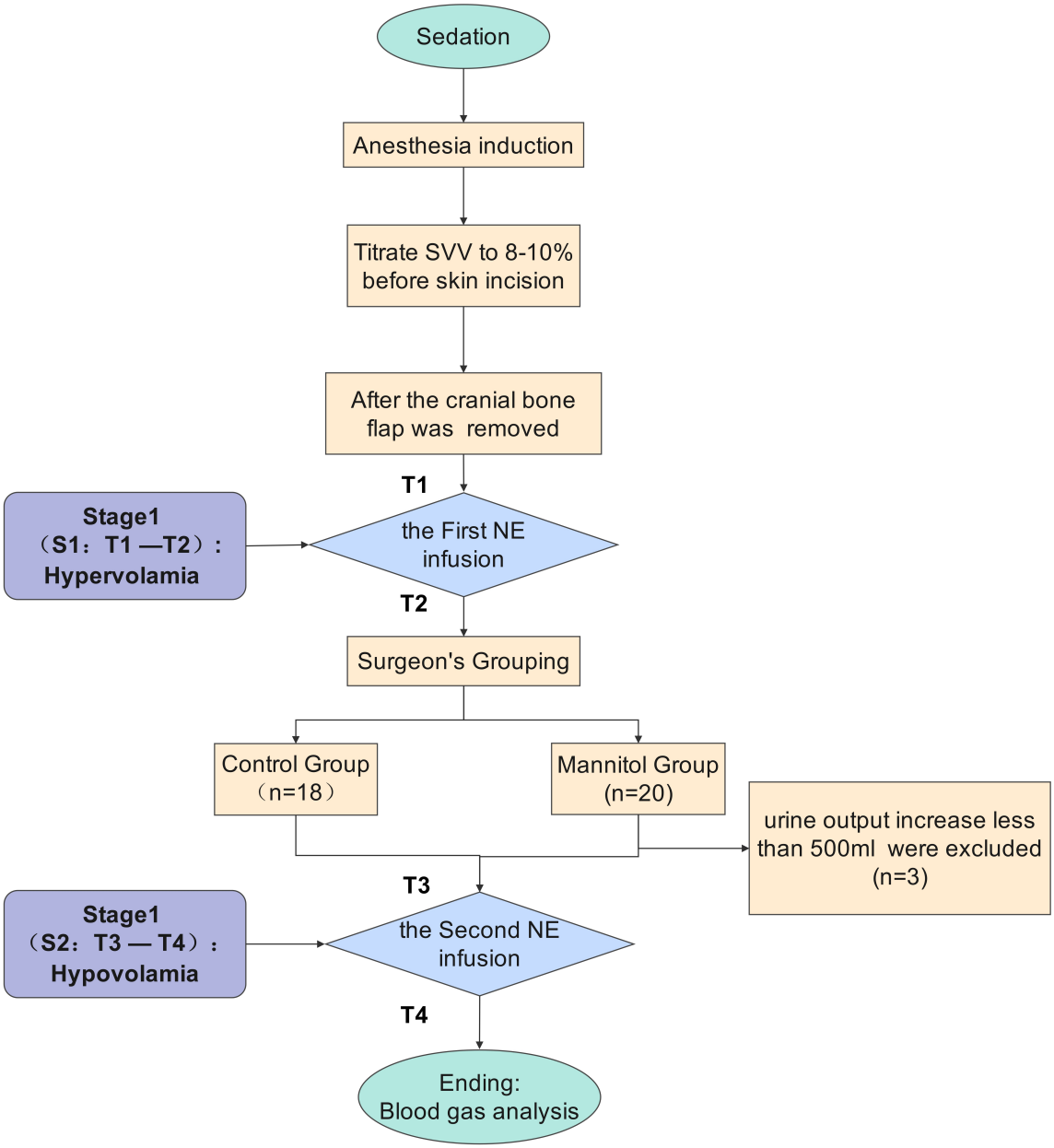


Figure 2. The experimental protocols and workflow. Note: NE: Norepinephrine; S1: stage 1; S2: stage 2.

eterization was conducted for FloTrac/Vigileo monitoring system (Version 3.02; Edwards Lifesciences, Irvine, CA, USA).

Study protocol

The study protocol was depicted in detail in **Figure 2**. Prior to skin incision, SVV to 8-10% was titrated by crystalloid infusion. The crystalloid infusion was initiated as 2-4 mL/kg/h. After the skull was completely opened, participants were assigned to either Mannitol Group (Group M) or Control Group (Group C) according to the surgical demands. Surgeons allocated patients based on their routine practice or the extent of cerebral swelling upon dural opening, with no interventions from the anesthesiologists. In the Mannitol group, 0.5 g/kg mannitol was rapidly infusion within 15 min through the central venous, while in the Control group, normal saline (N.S.) was infusion instead.

Two distinct intravascular volume phases-hypervolemia before mannitol infusion and hypovolemia after mannitol administration-were defined by CVP and urine output measurement. Specifically, the phase before mannitol or N.S. infusion was defined as the hypervolemia stage (Stage 1, S1), and the phase after infusion as the hypovolemic stage (Stage 2, S2). T1 and T2 denote the onset and termination of S1, whereas T3 and T4 denote the onset and termination of S2. During two phases, NE was pumped via a dose-increasing titration protocol (initial dose: 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, dose increment: 0.01-0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, ceiling dose: 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, time interval: 1-2 minutes, adjusted according to the blood pressure).

In detail, T1 for both groups was set upon dural opening and when MAP dropped by approximately 10% from baseline. In the Mannitol Group, T3 was set at when urine output exceeded 500 mL after mannitol infusion. In the Control Group, T3 was set at 1.5 hours after N.S. infusion. T2 and T4 in both groups were set at when MAP rose about 20% above baseline after NE infusion.

Hemodynamic management and clinical safety

The two NE infusion periods were scheduled to fall in the intraoperative hypotension episodes. During stage 1 (S1, T1-T2), after the skull is fully opened, a transient hypotension often occurs due to the loss of compression and the absence of nociceptive nerves of brain tissue. During stage 2 (S2, T3-T4), rapid mannitol infusion typically induces marked blood pressure reduction secondary to substantial diuresis.

Continuous invasive arterial blood pressure monitoring was performed throughout the surgery, with blood pressure fluctuations restricted to within ± 20% of the preoperative baseline.

The trial protocol would be terminated in cases of massive intraoperative hemorrhage, or if the surgeon identified acute complications including severe cerebral edema or midline shift.

Upon completion of the study protocol, blood gas analysis was promptly performed to assess the tissue perfusion, followed by supportive interventions such as fluid resuscitation.

Bias control

To minimize the bias induced by NE dose adjustment, after each dose adjustment, hemodynamic variables were recorded once all parameters had reached full stabilization following each dose adjustment.

SVV was titrated to 8-10% prior to study initiation to ensure a balanced baseline fluid status across all patients.

To ensure an adequate diuretic effect of mannitol, patients in the mannitol group whose urine output increased by less than 500 mL within 1.5 hours after mannitol infusion were excluded from subsequent analyses.

During data analysis, all data analysts were blinded to group allocation.

Outcome measures

Primary outcomes: Stroke volume (SV), systolic blood pressure (SBP), CI (cardiac index) and SVV were continuously monitored by FloTrac/Vigileo system from T1 to T2 and T3 to T4. CVP and urine output were recorded at T1 and T3. Blood lactate and blood glucose were measured before leaving the operation room.

Secondary outcomes: Intraoperative outcomes including total blood loss, urine output, total fluid intake and output, surgical duration, recovery duration, and brain relaxation score (BRS). Postoperative outcomes including Glasgow Coma Scale (GCS) scores on admission and at discharge, total hospital stay, and postoperative adverse events. The 30-day postoperative outcomes including the Glasgow Outcome Scale (GOS) score, mortality, re-operation, and re-admission occurrence. Bedside follow-up was performed by attending anesthesiologists on postoperative days 2 and 7. Discharge-GCS were fully recorded in the medical record system by surgeons. Glasgow Outcome Scale (GOS) at 30 days after surgery was conducted by attending anesthesiologists through telephone follow-up.

Brain Relaxation Score (BRS) at dural closure were assessed by neurosurgeon's visual and tactile assessment using a validated 4-point scale (1 = excellent relaxation, 2 = adequate relaxation, 3 = tense brain, 4 = brain bulging). BRS 1 and 2 were taken as satisfactory brain relaxation, whereas BRS ≥ 3 were taken as inadequate brain relaxation [1].

The GCS scores were conducted by attending surgeon based on three components: eye opening, verbal response, and motor response, with summed scores ranging from 3 to 15. GCS was categorized into mild (13-15), moderate (9-12), and severe (3-8) categories.

The Glasgow Outcome Scale (GOS) is a five-level scale for assessing long-term functional outcomes after brain injury. Score 1: death attributable to brain injury or its complications. Score 2: persistent vegetative state, with stable vital signs and intact sleep-wake cycles but no awareness, effective communication or purposeful movement. Score 3: severe disability, with preserved consciousness but severe neurological deficits and total dependence on daily care. Score 4: moderate disability, with independent self-care ability but residual neurological impairment limiting pre-injury work and social participation. Score 5: good recovery, with full return to daily work and social life, and minor symptoms that do not affect functional activity.

Statistical analysis

All data were extracted from the anesthesia information system (Digi-healthy System) in our hospital. Statistical analyses were performed by GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA) and BM SPSS Statistics Version 31.0 (IBM Corp, Armonk, NY, USA). Normality of quantitative data was assessed by Shapiro-Wilk test. Continuous variables conforming to normal distribution were expressed as mean ± standard deviation (SD), while conforming to non-normal distribution were described as median (interquartile range, IQR). Comparisons of normal distribution between the two groups were analyzed by independent t-test, and three or more groups were analyzed by one-way ANOVA, and intra-group pairwise comparisons (pre vs post intervention) were analyzed by paired t-test. Comparisons of non-normal distribution between two groups were analyzed by Mann-Whitney U test, and three or more groups were performed by the Kruskal-Wallis H test, and intra-group pairwise comparison was analyzed by Wilcoxon signed-rank test. Categorical data were expressed as frequencies, and were analyzed by chi-square test (each cell was ≥ 5) or Fisher's exact test (one cell < 5). Comparisons of slopes and intercepts among linear regression equations were performed by Analysis of Covariance (ANCOVA). Logistic regression analysis was performed to identify independent risk factors for postoperative complications. Receiver operating characteristic (ROC) curves were plotted as S2 of the Mannitol Group which served as the hypovolemia gold standard, and S1 of the Control group served as the hypervolemia gold standard. Area under the receiver operating characteristic curve (AUC) were calculated and compared for diagnostic performance. A two-tailed significance level of $\alpha = 0.05$ was adopted; $P < 0.05$ was considered statistically significant.

Results

A total of 65 patients undergoing selective craniotomy were recruited for this trial. Ten patients were excluded upon screening: 3 with vulnerable brain, 4 who refused SVV monitoring, and 3 in Mannitol Group with inadequate urine output. The remaining 55 patients were enrolled consecutively, with the first 35 cases assigned to the training cohort and the subsequent 20 cases to the validation cohort (**Figure 1**). No patients were lost to postoperative follow-up.

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics of Training cohort and Validation cohort and between Control and Mannitol sub-groups are presented (**Tables 1**, **2**). There were no statistically significant intergroup differences in sex, age, BMI, ASA classification, tumor type, tumor size, tumor location, GCS scores and preoperative comorbidities (all $P > 0.05$). All comorbidities were adequately controlled before surgery.

Assessment of volume status in both groups during hypervolemia and hypovolemia stages

Two distinct phases were defined according to the alterations of intravascular volume before

Table 1. Baseline demographic and clinical characteristics of training cohort and validation cohort

	Training cohort (*n* = 35)	Validation cohort (*n* = 20)	*P* Value
Sex (M/F, n)	16/14	13/12	> 0.999
Age (years)	53.07 ± 15.39	53.24 ± 10.13	0.960
BMI (kg/m^2)	21.64 ± 3.927	24.46 ± 4.576	0.019
ASA classification (I/II/III)	15/9/6	17/4/4	0.399
Tumor type (Glioma/Meningioma/pituitary/Metastasis/others)	3/9/7/3/8	5/3/7/3/7	0.553
Tumor size (cm^2)	14.49 ± 11.11	19.48 ± 13.40	0.234
Tumor location (Supra/infra-tentorial)	20/15	10/10	0.779
GCS scores	15 (15, 15)	15 (15, 15)	0.269
GCS category	29/1/0	22/3/0	0.320
Comorbidity			0.265
Hypertension	5	8	
Diabetes	3	0	
Pulmonary disease	3	3	
Others	4	1	

Note: BMI: Body mass index; ASA: American Society of Anesthesiologists; GCS: Glasgow Coma Scale.

and after mannitol infusion: a hypervolemia (Stage1: S1, T1-T2) and a hypovolemia respectively (Stage1: S2, T3-T4). Central venous pressure (CVP) and urine output were adopted to determine the hypovolemic status. The Mannitol Group exhibited significantly greater alterations in CVP and urine output compared with the Control Group. From S1 to S2, the Control Group showed a slight increase of 0.05 ± 0.9 cm H_2O in CVP, accompanied by an increase of 154 ± 36 ml in urine output. In comparison, the Mannitol Group showed a reduction of 1.8 ± 0.4 cm H_2O in CVP, alongside a marked increase of 587 ± 82 ml in urine output (**Figure 3**). In the Mannitol Group, patients with urine output increase < 500 ml within 1.5 h after mannitol infusion were defined as inadequate hypovolemia and were excluded.

Hemodynamic changes during norepinephrine infusion in the two groups in hypervolemic and hypovolemic stages

Our previous work showed that repeated rapid NE boluses induced marked and long-lasting disturbances in SVV, SV, and CI, which failed to fully recover after NE cessation [23]. In contrast, slow titration of continuous NE infusion allowed complete restoration of theses parameters. Accordingly, we implemented a gradual dose-escalation NE regimen in this trial. With the gradual increase in NE infusion dosage, serial changes of SV, SBP, CI and SVV from T1 to T4 are presented (**Figure 4** shows two representative patients: Case 1 from the control group; Case 2 from the mannitol group. **Figure 5** shows the overall dynamic shifts of two groups in two stages). All patients shared similar hemodynamic tendencies: with the gradual increase in NE infusion dosage, SBP elevated and SVV lowered markedly, while SV and CI rose slightly with substantial individual differences. Subgroup analyses indicated significant S1-S2 differences in SV, SBP, CI and SVV within the Mannitol Group, yet no analogous inter-stage differences within the Control group.

Correlations of CI, SV, SBP and norepinephrine dosage with SVV and regression models of SVV

To establish a corrective formula for SVV, we analyzed the correlations between SVV and other hemodynamic parameters as well as NE dosage. SVV exhibited a strong negative correlation with SBP (r = -0.86, P < 0.01), a moderate negative correlation with SV (r = -0.36, P < 0.01), a weak negative correlation with CI (r = -0.22, P < 0.01), and a moderate negative correlation with NE dosage (r = -0.55, P < 0.01) (**Figure 6**). Multivariate linear regression analysis was conducted with SVV designated as the dependent variable, and CI, SV, SBP as well as NE dosage incorporated as independent variables. The regression equation was (P < 0.001, R^2 = 0.745):

Table 2. Baseline demographic and clinical characteristics of training cohort and validation cohort between control and mannitol sub-groups

	Training cohort (*n* = 35)			Validation cohort (*n* = 20)		
	Control (*n* = 18)	Mannitol (*n* = 17)	*P* Value	Control (*n* = 12)	Mannitol (*n* = 8)	*P* Value
Sex (M/F)	9/9	10/7	0.738	7/5	3/5	0.650
Age (years)	52.11 ± 16.79	54.24 ± 10.60	0.072	54.50 ± 13.60	51.13 ± 9.37	0.520
BMI (kg/m^2)	20.93 ± 3.91	23.92 ± 4.80	0.409	22.71 ± 3.86	25.63 ± 4.10	0.132
ASA classification (I/II/III)	10/6/2	12/3/2	0.696	5/3/4	5/1/2	0.717
Tumor type (Glioma/Meningioma/pituitary/Metastasis/others)	3/5/4/1/5	4/2/7/0/4	0.595	0/4/3/2/3	1/1/0/3/3	0.295
Tumor size (cm^2)	11.37 ± 8.19	15.68 ± 12.06	0.367	19.43 ± 12.96	20.24 ± 13.94	0.911
Tumor location (Supra/infra-tentorial)	10/8	10/7	0.999	5/7	5/3	0.650
GCS scores	15 (15, 15)	15 (15, 15)	0.478	15 (15, 15)	15 (15, 15)	0.400
GCS category (mild/moderate/severe)	17/1/0	15/2/0	0.603	12/0/0	7/1/0	0.400
Comorbidity			0.360			0.675
Hypertension	3	6		2	2	
Diabetes	2	0		1	0	
Pulmonary disease	1	3		2	0	
Others	3	1		1	0	

Note: BMI: Body mass index; ASA: American Society of Anesthesiologists; GCS: Glasgow Coma Scale.

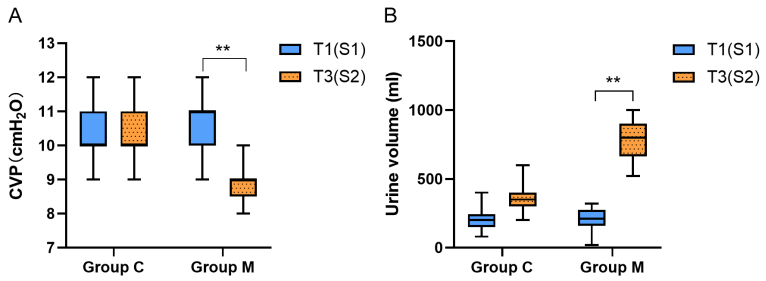


Figure 3. CVP and cumulative urine output of the two groups during S1 and S2 (Training cohort: Control group: n = 18; Mannitol group: n = 17). A. The CVP values in the two groups at T1 and T3; B. The cumulative urine output in the two groups at T1 and T3. $^{**}P < 0.01$ indicates a statistically significant difference. Note: CVP: Central venous pressure; S1: stage 1 (T1-T2), hypervolemia; S2: stage 2 (T3-T4), hypovolemia.

for each participant. All patient-level regression equations were subjected to the intergroup comparison (**Figure 7**). The piecewise linear regression formulas for each subgroup are listed below:

Group C-S1: $Y = -0.102X + 19.96$ ($P < 0.01$, $R^2 = 0.806$); Group C-S2: $Y = -0.100X + 19.77$ ($P < 0.01$, $R^2 = 0.771$); Group M-S1: $Y = -0.097X + 19$ ($P < 0.01$, $R^2 = 0.732$); Group M-S2: $Y = -0.106X + 21.18$ ($P < 0.01$, $R^2 = 0.781$).

$SVV = 21.03 - 0.0271 \times CI - 0.011 \times SV - 0.100 \times SBP - 0.005 \times NE$

Full regression parameters are presented in **Table 3**. There was no evident multicollinearity between variables, and residual normality was satisfied. Results showed SBP possessed a significant independent impact on SVV, NE dosage and SV approached borderline significance, whereas CI failed to demonstrate any independent statistical correlation.

Since SBP possessed the most independent impact on SVV, a univariate linear regression model was built with SBP as the independent variable and SVV as the dependent variable: $SVV = 20.52 - 0.106 \times SBP$ ($R^2 = 0.739$, $P < 0.001$). Then the SBP-adjusted SVV residuals were taken as the dependent variable, CI, SV, and NE dosage were taken as the independent variables, separate univariate linear regression models were constructed. The regression coefficients for each model are summarized in **Table 4**. Results showed that SBP alone accounted for 73.9% of the total variance in SVV. Although NE dosage reached statistical significance, it only explained 0.3% of the variance in SBP-adjusted SVV residuals ($R^2 = 0.003$). So, this demonstrated that SBP is predominant in the SVV fluctuations.

The SBP-SVV curves of the two groups in hypervolemic and hypovolemic stages

Considering the substantial inter-individual heterogeneity in baseline SBP and SVV among patients, a subject-specific linear regression model between SBP and SVV were generated ANCOVA further revealed comparable slopes ($P = 0.495$) but significantly different intercepts ($P < 0.01$) across four fitted curves. The aggregate pooled slope across all subgroups was -0.101.

Derivation and validation of BpSVV

Mathematical derivation of BpSVV: Since the SBP-SVV regression curve exhibited a negative linear association with a pooled slope of -0.101, based on mathematical principles, the ΔSBP-ΔSVV also follows a negative linear relationship with the same slope. Therefore, ΔSBP can be used to quantify ΔSVV for the correction of raw SVV. So the corresponding corrective equation could be expressed as: SVV = 0.101 × ΔSBP + raw SVV. We designated this corrective SVV as BpSVV, yielding the final formula: BpSVV = 0.101 × ΔSBP + raw SVV. We hypothesize that BpSVV could serve as a novel indicator for evaluating the intravascular volume during NE infusion.

Clinical validation of BpSVV: To verify the diagnostic performance of BpSVV, we included the remaining 20 subjects in the validation set and compared two indicators: raw SVV before NE infusion (T1 and T3) and BpSVV after NE infusion (T2 and T4). In the Mannitol group, both raw SVV and BpSVV increased significantly from S1 to S2 (T3 versus T1 and T4 versus T2) (both P < 0.001). In contrast, no differences were detected in the Control group. To assess the diagnostic efficacy of the two indicators, stage S2 of the Mannitol group was taken as the gold standard for dehydration and hypovolemia, and Receiver Operating

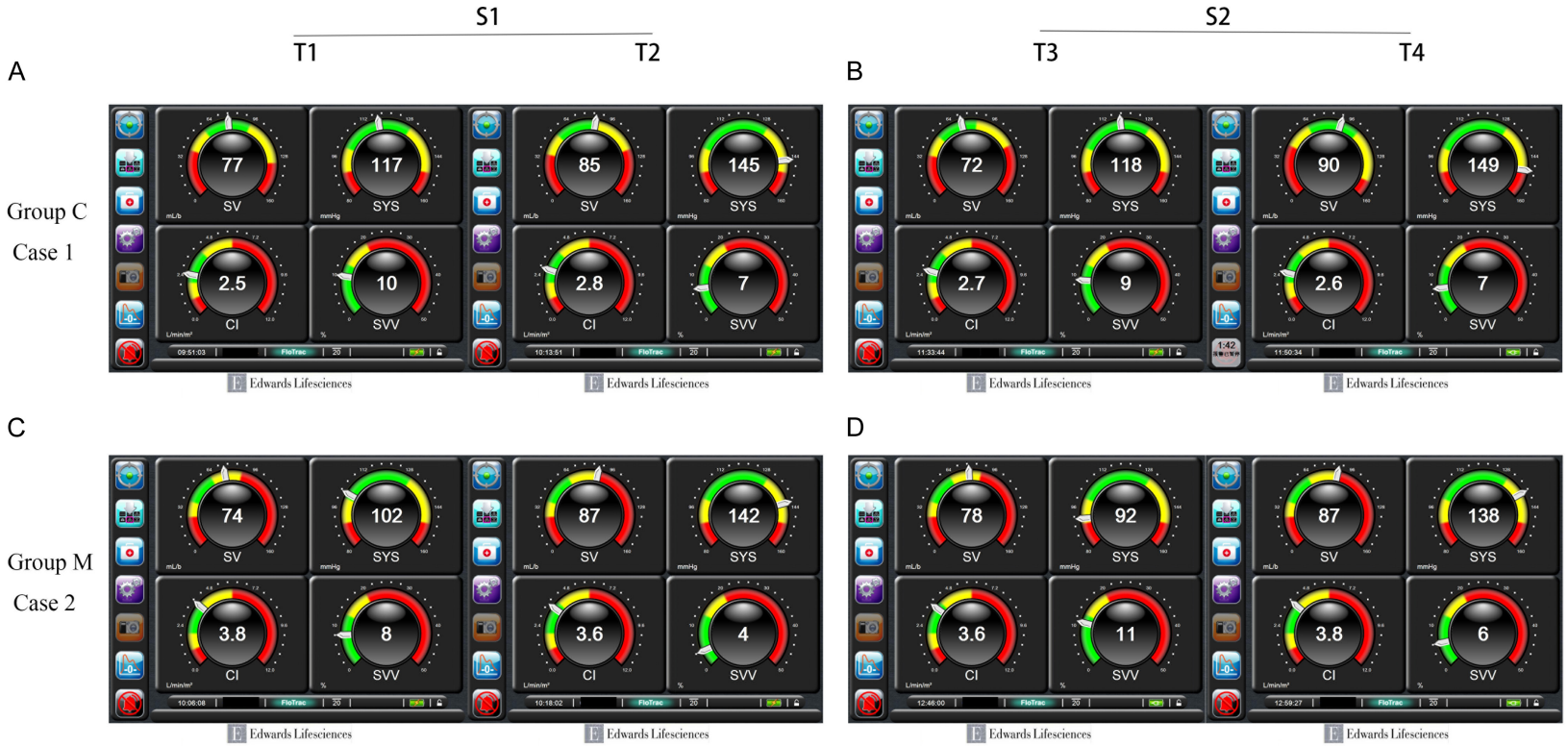


Figure 4. The SV, SBP, CI and SVV values of two representative cases from both groups from T1 to T4. (Training cohort: Control group: n = 18; Mannitol group: n = 17). A. The hemodynamic changes of case 1 in stage 1 (T1-T2). B. The hemodynamic changes of case 1 in stage 2 (T3-T4). C. The hemodynamic changes of case 2 in stage 1 (T1-T2). D. The hemodynamic changes of case 2 in stage 2 (T3-T4). Note: SV: stroke volume; SBP: systolic blood pressure; CI: cardiac index; SVV: stroke volume variation; S1: stage 1 (T1-T2), hypervolemia; S2: stage 2 (T3-T4), hypovolemia.

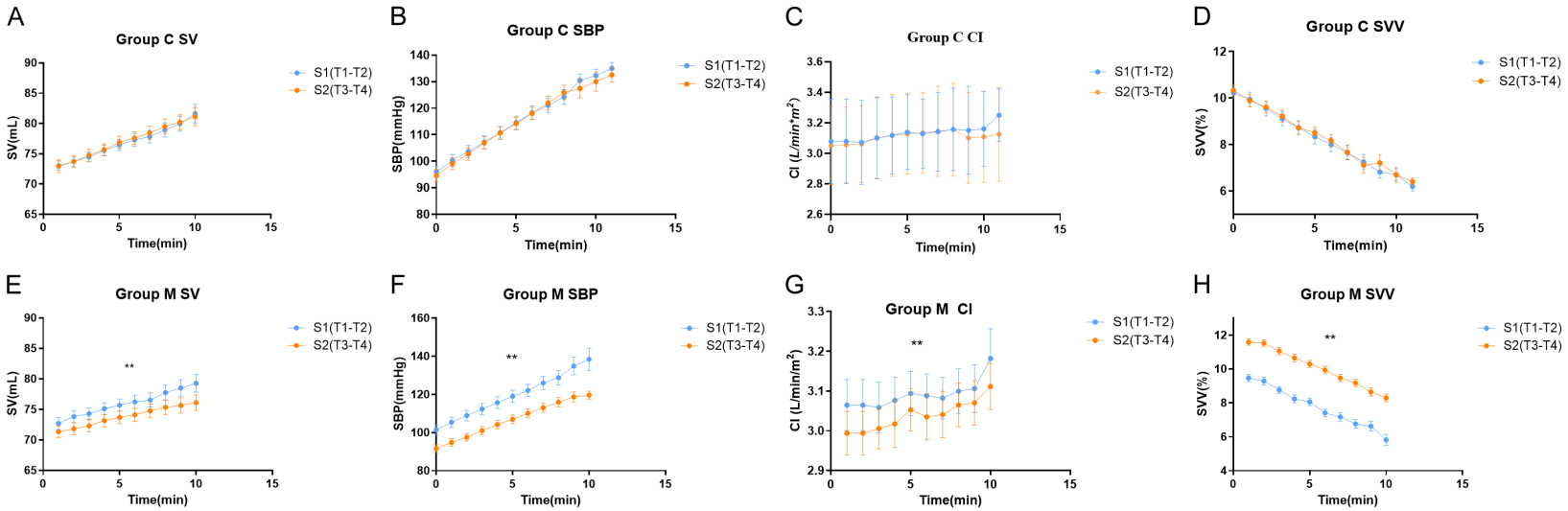


Figure 5. Summarized dynamic changes in SV, SBP, CI, and SVV of the two groups during S1 and S2 (Training cohort: Control group: n = 18; Mannitol group: n = 17). A-D. Time-course changes of SV, SBP, CI, and SVV in control group. E-H. Time-course changes of SV, SBP, CI, and SVV in mannitol group. $^{**}P < 0.01$ indicates a statistically significant difference. Note: SV: stroke volume; SBP: systolic blood pressure; CI: cardiac index; SVV: stroke volume variation; S1: stage 1, hypervolemia; S2: stage 2, hypovolemia.

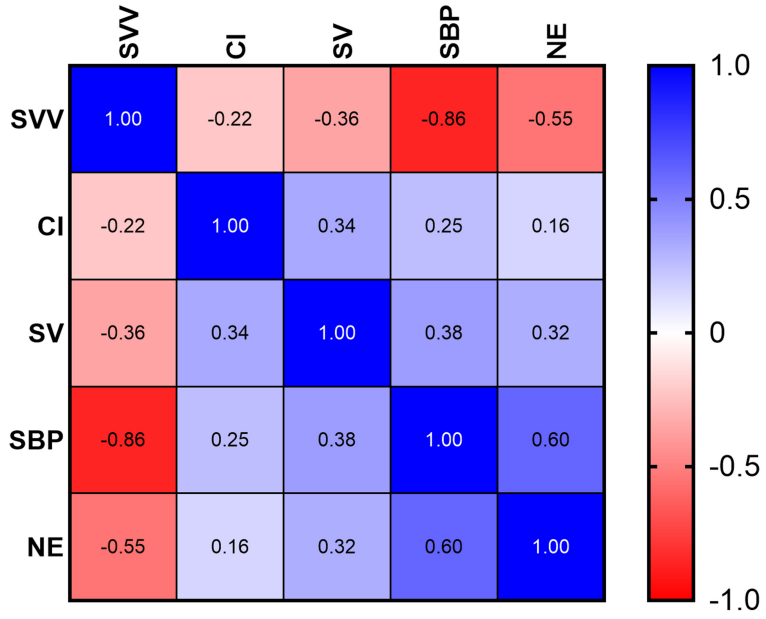


Figure 6. Pearson correlation coefficient matrix of SVV, CI, SV, SBP and NE dosage (Training cohort: Control group: n = 18; Mannitol group: n = 17, all $P < 0.05$). Note: SV: stroke volume; SBP: systolic blood pressure; CI: cardiac index; SVV: stroke volume variation; NE: norepinephrine.

Characteristic curves (ROC) for ΔrawSVV and ΔBpSVV were plotted. The Area Under the Curve (AUC) was 0.9531 (95% CI, 0.8699-1.000) for Δraw SVV and 0.9167 (95% CI, 0.7854-1.000) for ΔBpSVV, demonstrating comparable diagnostic efficacy of the two indices (**Figure 8**).

Comparison of intraoperative and postoperative clinical data between the two groups

The intraoperative profiles, postoperative clinical outcomes, and peak NE doses were summarized in **Table 5**. Postoperative complications were categorized into neurological and non-neurological events with detailed enumeration. No cases of postoperative death, 30-day reoperation or 30-day readmission occurred in this study.

Finally, binary logistic regression models were constructed to analyze the impacts of various preoperative and intraoperative factors on neurological prognosis and non-neurological prognosis (**Figures 9**, **10**). It showed that preoperative ASA physical status classification, intraoperative blood glucose levels, and preoperative comorbidities exhibited marginally significant associations with non-neurological adverse events. The preoperative GCS category served as a statistically significant risk factor for neurological adverse events, whereas preoperative tumor size showed a marginal significance.

Discussion

During neurosurgical procedures, either excessive or inadequate fluid administration may exacerbate cerebral edema. SVV monitoring is widely utilized especially for prolonged neurosurgical anesthesia. Current neurosurgical anesthesia guidelines state that, adequate cerebral perfusion could be guaranteed when intravascular volume is optimized and MAP is maintained above 60-70 mmHg [24]. A broad consensus across noncardiac surgery states that MAP fluctuation should be limited to within ± 20% of the preoperative baseline [25]. In our study, all participants exhibited consistent responsiveness to NE, which is likely attributable to three key factors: titrating SVV to 8-10% with crystalloid before research, low-dose of mannitol (0.5 g/kg) infusion, and excluding patients with severe diabetes mellitus. The maximum NE dose in our study was below 0.1 μg/kg/min, which falls within the low-dose range according to the previous studies [14, 26, 27]. Arterial blood gas analysis and blood glucose levels further confirmed the sufficient cerebral perfusion in our study.

Numerous studies have demonstrated that NE infusion markedly decreases PPV and SVV, yet its effects on cardiac output (CO) and global end-diastolic volume (GEDV) remain highly controversial [6, 14, 28]. Some studies have observed that a low-dose of NE slightly raises cardiac output by weak β_1-adrenergic agonism effects, but high-dose of NE predominantly activate α_1-adrenergic receptors, boosting systemic vascular resistance and triggering reflexive bradycardia [13, 15]. In our study, with NE dosage increasing, SBP rose progressively

Table 3. Multiple linear regression analysis for predictors of SVV

Variables	β coefficient	95% CI	*P* value	VIF
CI	-0.027	-0.311-0.257	0.851	1.150
SV	-0.011	-0.027-0.004	0.152	1.283
SBP	-0.100	-0.106-0.095	< 0.001***	1.717
NE	-0.005	-0.009-0.001	0.015*	1.604

Note: R^2 = 0.7436, ***P < 0.001, *P < 0.05. Note: SV: stroke volume; SBP: systolic blood pressure; CI: cardiac index; SVV: stroke volume variation; NE: norepinephrine (Training cohort: Control group: n = 18; Mannitol group: n = 17).

Table 4. Univariate linear regression analyses of SBP-adjusted SVV residuals against CI, SV and NE dosage

Variables	β coefficient	95% CI	*P* value	R^2
CI	-0.052	-0.317-0.213	0.700	0.000
SV	-0.004	-0.018-0.010	0.565	0.000
NE	-0.003	-0.006-0.001	0.102	0.003

Note: Training cohort: Control group: n = 18; Mannitol group: n = 17. SV: stroke volume; SBP: systolic blood pressure; CI: cardiac index; SVV: stroke volume variation; NE: norepinephrine.

and SVV decreased gradually, but SV and CI altered slightly with substantial inter-individual variability, which is highly consistent with the findings of previous studies.

Our results revealed a negative linear correlation between SBP and SVV as NE dosage increasing. We thought this phenomenon could be explained by the pharmacological characteristics of NE and the fundamental cardiovascular hemodynamics formulas [26, 27, 29]. The equation of systemic vascular resistance (SVR) is: $SVR = \frac{MAP - RAP}{CO}$. Substituting the cardiac output equation $CO = SV \times HR$ to SVR formula and re-arranging yields: $SV = \frac{MAP - RAP}{SVR \times HR}$. Since RAP averages merely 5 mmHg, which is negligible compared with other indicators, the formula can be simplified to: $SV = \frac{MAP}{SVR \times HR}$. Since the FloTrac/Vigileo system computes SVV based on the peripheral artery sampling, actually the SVV measured is peripheral artery SVV(SVV_{pr}), that is, $SVV_{pr} = \frac{\Delta SV_{pr}}{SV_{pr}}$. We defined parameter I as the peripheral blood flow distribution coefficient relative to the whole vascular compartment, that is, $SV_{pr} = I \times SV$. Combing $SV = \frac{MAP}{SVR \times HR}$ with $SVV_{pr} = \frac{\Delta SV_{pr}}{SV_{pr}}$ yields: $SVV_{pr} = \frac{\Delta SV_{pr}}{I \times SV} = \frac{\Delta SV_{pr} \times SVR \times HR}{MAP \times I} = \frac{1}{MAP} \times \frac{SVR}{I} \times HR \times \Delta SV_{pr}$. The full derivation process is illustrated in **Figure 11**.

Based on the pharmacological characteristics of NE, low dose of NE exerts prominent influences on MAP, SVR, and parameter *I*, but minimal effects on HR [26-28]. Since ΔSV_{pr} is relatively small and HR is barely affected by NE, so $HR \times \Delta SV_{pr}$ could be taken as a constant value K. Then the formula $SVV_{pr} = \frac{1}{MAP} \times \frac{SVR}{I} \times HR \times \Delta SV_{pr}$ could be simplified to: $SVV_{pr} = \frac{K}{MAP} \times \frac{SVR}{I}$. From a mathematical perspective, $SVV_{pr} = \frac{K}{MAP}$ is a standard inverse proportional equation with MAP as the independent variable, and its slope decreases drastically as MAP increases. As NE dosage increasing, SVR rises sharply whereas parameter *I* declines markedly, so $\frac{SVR}{I}$ will increase furthermore. When $SVV_{pr} = \frac{K}{MAP}$ is multiplied by $\frac{SVR}{I}$ - a coefficient that increases sharply as MAP rising - the declining slope will get great compensation and tend to be stable. Finally, the equation $SVV_{pr} = \frac{1}{MAP} \times \frac{SVR}{I} \times K$ may approach to a negative linear formula $SVV = -\kappa \times SBP + b$ with its slope stable, which is consistent with our study. The process of equation derivation and conversion is illustrated in **Figure 12**.

With respect to the clinical implication of formula BpSVV = SVV + 0.101 × ΔSBP, we propose that it can effectively quantify the independent confounding bias of NE dosage on SVV by incorporating SBP rising, which could be tentatively used to correct the raw SVV. We consider that the superiority of BpSVV is mainly manifested during NE infusion with dose adjustments, as raw SVV is perturbed and unreliable. Therefore, BpSVV retains clinical advantages for hemodynamic assessment.

Numerous clinical trials have demonstrated that a single infusion of mannitol at 0.5 g/kg produces no significant influence on long-term neurological function, cerebral organic injury, or tumor-associated prognosis, whose long-term outcomes were predominantly determined by the tumor grade, extent of resection, and preoperative neurological baseline [17, 18, 30]. Consistent with these studies, we found no effect of mannitol infusion on both neurological and non-neurological outcomes. In contrast, neurological complications were

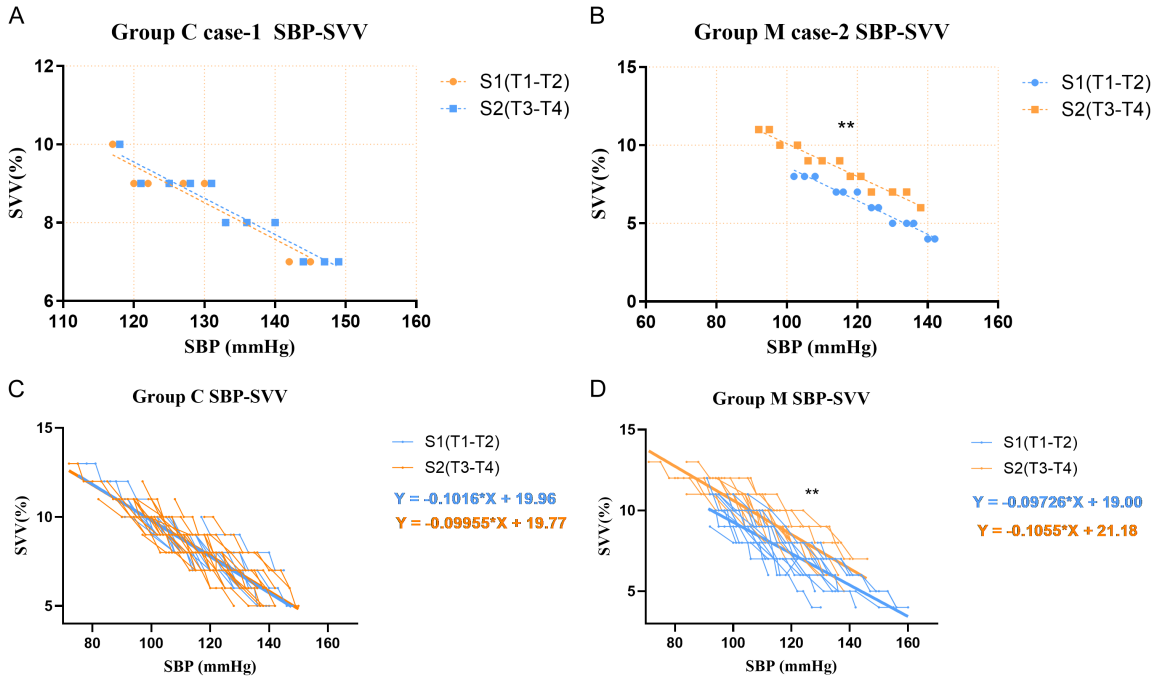


Figure 7. The SBP-SVV curves of the two groups during S1 and S2 (Training cohort: Control group: n = 18; Mannitol group: n = 17). A, B. The SBP-SVV curve of Case 1 and Case 2 in S1 and S2 respectively. C, D. The summarized SBP-SVV curve of two groups in S1 and S2 respectively. $^{**}P < 0.01$ indicates a statistically significant difference. Note: SBP: systolic blood pressure; SVV: stroke volume variation; NE: norepinephrine; S1: stage 1, hypervolemia; S2: stage 2, hypovolemia.

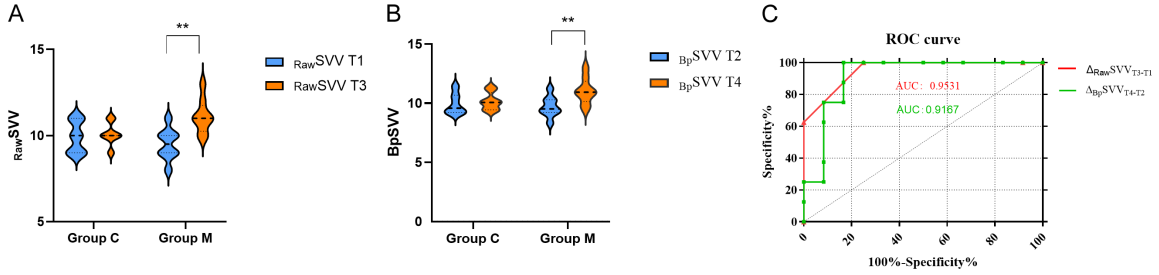


Figure 8. Comparison of diagnostic performance of SVV and BpSVV between the two groups during S1 and S2 (Validation cohort: Control group: n = 12; Mannitol group: n = 8). A. The $_{Raw}$SVV of two groups at T1 and T3. B. The BpSVV of the two groups at T2 and T4. C. ROC curves and AUC of Δ_{Raw}SVV and ΔBpSVV. $^{**}P < 0.01$ indicates a statistically significant difference. Note: NE: norepinephrine; SBP: systolic blood pressure; SVV: stroke volume variation; S1: stage 1 (T1-T2), hypervolemia; S2: stage 2 (T3-T4), hypovolemia; ROC: Receiver operating characteristic; AUC: curves and area under the curve.

primarily associated with the baseline GCS scores.

Limitations

There are some limitations in our study. Firstly, only a limited range of surgeries were included, restricting our protocol to low-dose NE infusion. Further research is required to verify the validity of this formula during high-dose NE infusion by other clinical models, including hepatectomy and hemorrhagic shock. Secondly, the sample size was constrained by the relatively low incidence of brain tumors at our center and the cost of SVV monitoring. Accordingly, we designed a self-controlled case-series study with serial bias control strategies to reduce the sample size. Thirdly,

Table 5. Intraoperative profiles and postoperative outcome

	Control (*n* = 35)	Mannitol (*n* = 20)	*P* Value
Maximum NE dose (ng/kg/min)	5.33 ± 0.71	8.16 ± 0.90	< 0.01**
Brain relaxation scores	1.44 ± 0.51	1.35 ± 0.49	0.593
Crystalloid infusion (ml)	2523 ± 968	2739 ± 1933	0.615
Colloid infusion (ml)	690 ± 249	794 ± 356	0.319
Total urine output (ml)	1254 ± 507	1668 ± 764	0.027*
Lactate Level (mmol/L)	2.16 ± 1.17	1.96 ± 0.85	0.492
Glucose Level (mmol/L)	7.56 ± 1.95	8.26 ± 1.53	0.492
Duration of surgery (min)	357 ± 135	411 ± 237	0.324
Recovery duration (min)	33.3 ± 22.5	30.0 ± 15.8	0.616
Hospital stays (days)	18.8 ± 9.27	20.1 ± 9.45	0.571
NICU stays (days)	2.87 ± 1.38	2.96 ± 1.65	0.823
Discharge GCS classification (mild/moderate/severe)	30/3/2	16/4/0	0.330
Non-Neurological events			0.999
Fever	2	1	
Pulmonary disease	2	1	
Reoperation	0	0	
Neurological events			0.628
Epilepsy	2	1	
GCS score decrease	4	4	
Intracranial infection	1	0	
Facial nerve palsy	0	1	
Postoperative 30-day GOS score (GOS-1-5)	0/0/2/3/30	0/0/0/4/16	0.330

Note: NE: norepinephrine; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale. *P < 0.05, **P < 0.01 indicates a statistically signifcant difference.

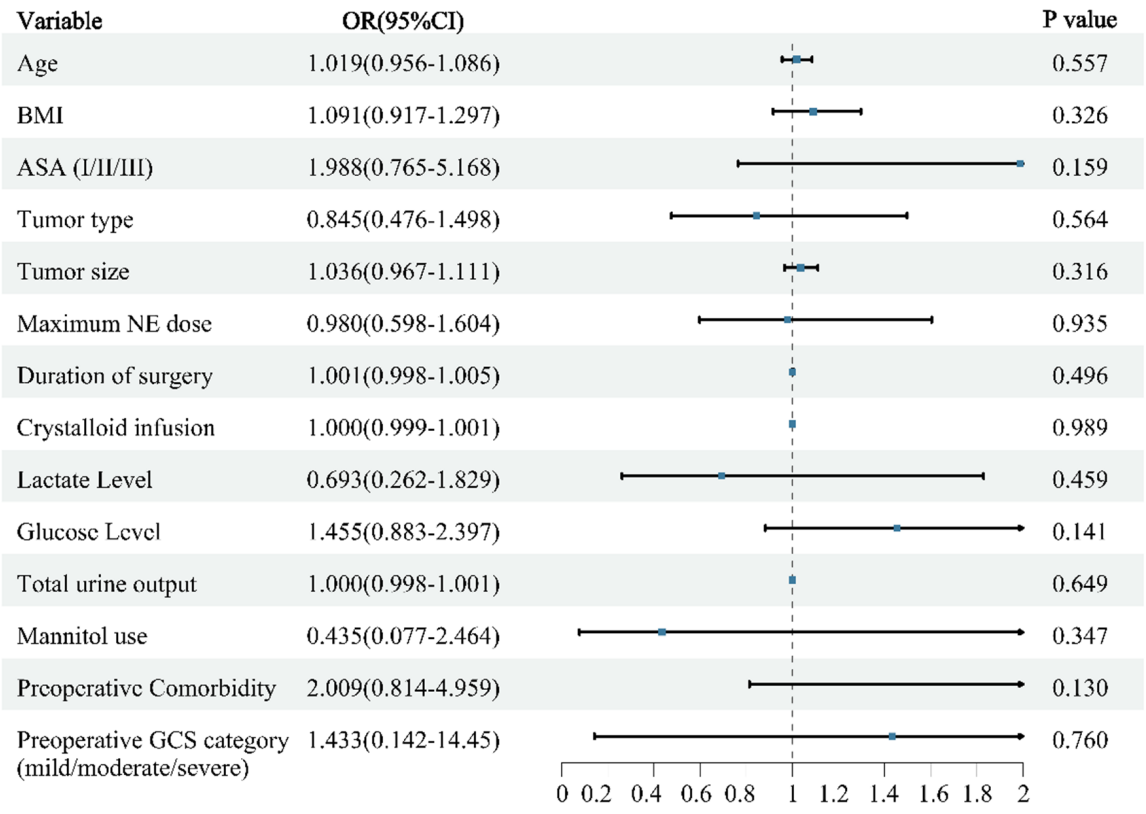


Figure 9. Forest plot of univariate logistic regression of related risk factors for non-neurological events. Note: BMI: Body mass index; ASA: American Society of Anesthesiologists; NE: norepinephrine; GCS: Glasgow Coma Scale.

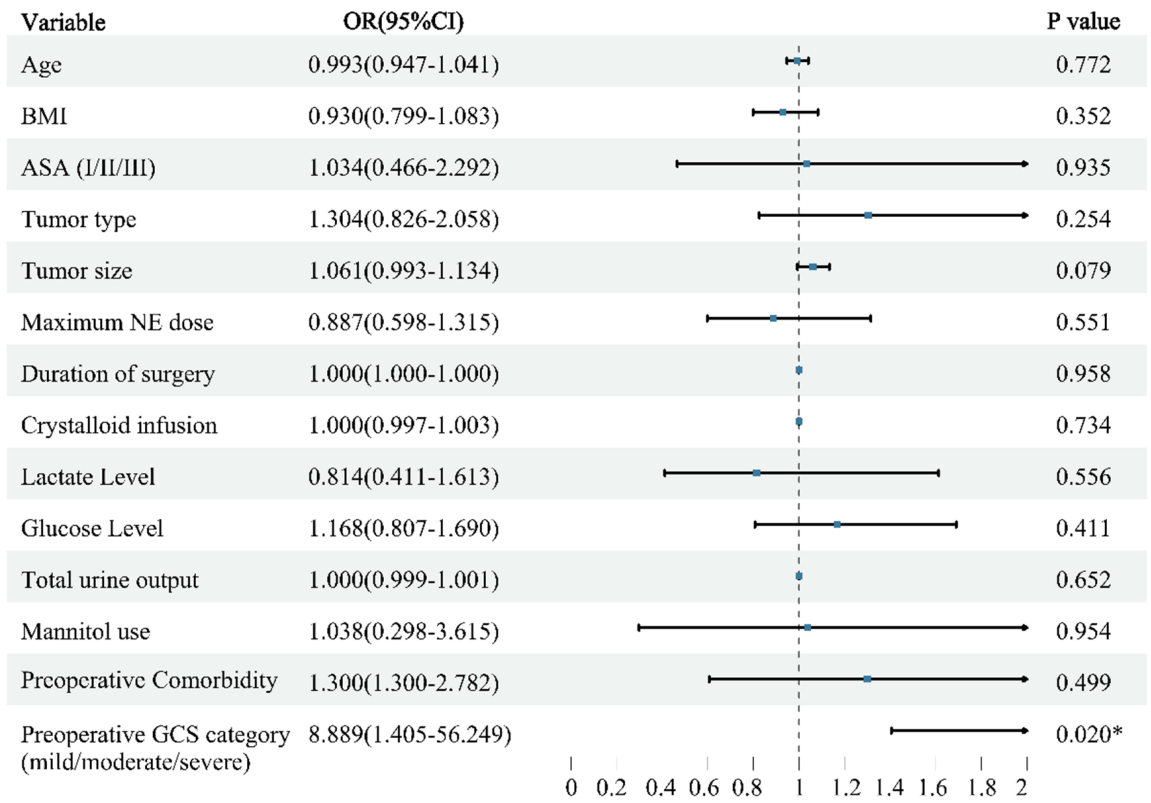


Figure 10. Forest plot of univariate logistic regression of related risk factors for Neurological events. *P < 0.05 indicates a statistically significant difference. Note: BMI: Body mass index; ASA: American Society of Anesthesiologists; NE: norepinephrine; GCS: Glasgow Coma Scale.

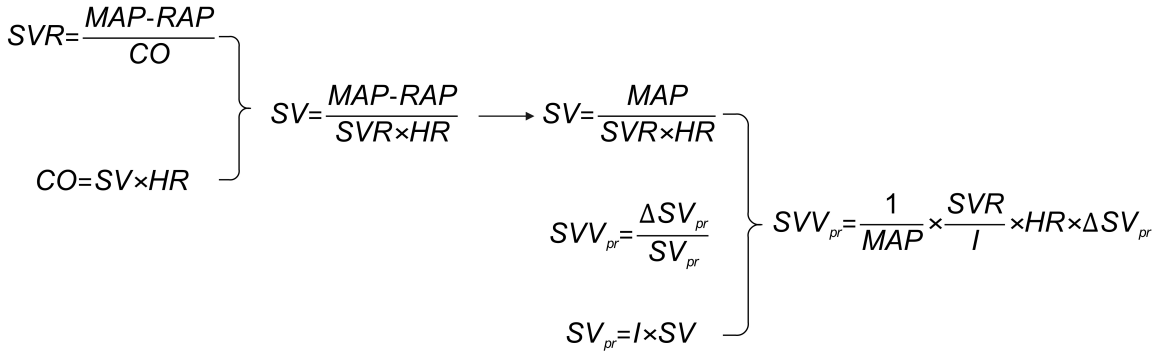


Figure 11. The mathematical derivation of $SVV_{pr}=\frac{1}{MAP}\times\frac{SVR}{I}\times HR\times\Delta SV_{pr}$ based on the pharmacological mechanism of norepinephrine and the formula of cardiovascular hemodynamics. Note: MAP: Mean arterial pressure; RAP: Right atrial pressure; CO: Cardiac output; SV: Stroke volume; HR: Heart rate; SVR: Systemic vascular resistance; I: Coefficient of peripheral distribution relative to total vascular blood flow.

we only investigated SVV obtained from the FloTrac/Vigileo system, because our pilot study had demonstrated that its sensitivity was superior to that of other SVV monitors.

Conclusion

We identified a negative linear relationship between SBP and SVV during NE infusion,

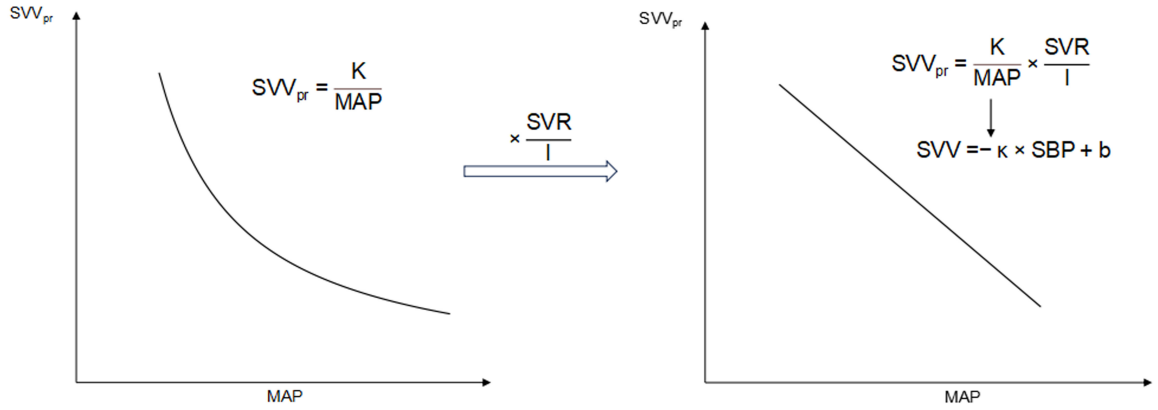


Figure 12. The formula evolution from an inverse proportional function $SVV_{pr} = \frac{1}{MAP} \times K$ to a negative linear function $SVV = -\kappa \times SBP + b$ by multiplying an increasing coefficient $\frac{SVR}{I}$. Note: MAP: Mean arterial pressure; SVR: Systemic vascular resistance; I: Coefficient of peripheral distribution relative to total vascular blood flow; K: $HR \times \Delta SV_{pr}$, a relative constant value.

which enables the mathematical quantification of NE-induced bias in SVV. By combining SBP and SVV to generate the newly derived parameter BpSVV, we established a practical corrective strategy for intravascular volume assessment that does not require NE cessation. This approach is particularly valuable in clinical settings where discontinuing NE infusion may pose potential safety risks. To enhance diagnostic accuracy, we recommend customizing the slope coefficient in the BpSVV formula according to the individual SBP-SVV correlation trends.

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Disclosure of conflict of interest

None.

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