Original Article

Cerebral autoregulation-directed optimal blood pressure management reduced the risk of delirium in patients with septic shock

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ABSTRACT

Background: When resuscitating patients with septic shock, cerebrovascular reactivity parameters are calculated by monitoring regional cerebral oxygen saturation (rSO_2) using near-infrared spectroscopy to determine the optimal blood pressure. Here, we aimed to analyze the impact of cerebral autoregulation-directed optimal blood pressure management on the incidence of delirium and the prognosis of patients with septic shock.

Methods: This prospective randomized controlled clinical study was conducted in the Xiangya Hospital of Central South University, China. Fifty-one patients with septic shock (December 2020–May 2022) were enrolled and randomly allocated to the experimental (n=26) or control group (n=25). Using the ICM$^+$ software, we monitored the dynamic changes in rSO_2 and mean arterial pressure (MAP) and calculated the cerebrovascular reactivity parameter tissue oxygen reactivity index to determine the optimal blood pressure to maintain normal cerebral autoregulation function during resuscitation in the experimental group. The control group was treated according to the Surviving Sepsis Campaign Guidelines. Differences in the incidence of delirium and 28-day mortality between the two groups were compared, and the risk factors were analyzed.

Results: The 51 patients, including 39 male and 12 female, had a mean age of (57.0±14.9) years. The incidence of delirium was 40.1% (23/51), and the 28-day mortality rate was 29.4% (15/51). The mean MAP during the first 24 h of intensive care unit (ICU) admission was higher ([84.5±12.2] mmHg *vs.* [77.4±11.8] mmHg, *P*=0.040), and the incidence of delirium was lower (30.8% *vs.* 60.0%, *P*=0.036) in the experimental group than in the control group. The use of cerebral autoregulation-directed optimal blood pressure (odds ratio [OR]=0.090, 95% confidence interval [CI]: 0.009 to 0.923, *P*=0.043) and length of ICU stay (OR=1.473, 95% CI: 1.093 to 1.985, *P*=0.011) were risk factors for delirium during septic shock. Vasoactive drug dose (OR=8.445, 95% CI: 1.26 to 56.576, *P*=0.028) and partial pressure of oxygen (PaO_2) (OR=0.958, 95% CI: 0.921 to 0.996, *P*=0.032) were the risk factors for 28-day mortality.

Conclusions: The use of cerebral autoregulation-directed optimal blood pressure management during shock resuscitation reduces the incidence of delirium in patients with septic shock.

Trial Registration: ClinicalTrials.gov ldentifer: NCT03879317

Introduction

Sepsis refers to the life-threatening organ dysfunction caused by a maladjusted host response to infection. Sepsis and septic shock are important global health problems that affect millions of people annually. Over the past three decades, the definition of sepsis has changed.[1-3] Although the Surviving Sepsis Campaign Guidelines, early goal-directed therapy, and treatment modalities have improved,[4-6] the mortality rate associated with septic shock remains high. The 30-day mortality rates associated with septic shock in Australia, Europe, and North America are 26.4%, 32.5%, and 33.7%, respectively.[7] In China, the mor-

tality rate is 37.3%.[8] In a recent cross-sectional survey conducted in China, the 28-day mortality rate was found to be 55.6%.[9] Septic shock is a heterogeneous condition that often affects multiple organ functions. The current guidelines recommend mean arterial pressure (MAP) ≥65 mmHg during shock resuscitation, but they are inappropriate for individualized and accurate treatment for different patients. Determining the optimal blood pressure for patients with septic shock is an important problem that needs to be addressed in clinical practice. With the development of technologies for monitoring cerebral autoregulation function, an individualized target blood pressure management scheme based on cerebrovascular reactivity parameters has been proposed in recent years; maintaining the MAP within the range of optimal cerebral perfusion pressure (CPPopt) ±5 mmHg was associated with better prognosis in patients with brain injury.[10] Therefore, we aimed to investigate the role of cerebral autoregulation-directed optimal blood pressure management in the prognosis of patients with septic shock.

Sepsis-associated delirium (SAD) is a cerebral manifestation commonly occurring in patients with sepsis.[11] The incidence of SAD in patients with sepsis is as high as 70%.[12] Delirium is associated with increased mortality, prolonged hospitalization, prolonged mechanical ventilation (MV), increased costs, and cognitive impairment after discharge. Additionally, it is an important determinant for decline in quality of life.[13] The underlying mechanisms of SAD involve neuroinflammation, cerebral perfusion insufficiency, blood brain barrier dysfunction, and neurotransmitter imbalances.[13,14] Patients with SAD have decreased cerebral vascular compliance and cerebral perfusion. Fluctuations in perfusion pressure and cerebral vascular autoregulation dysfunction are important risk factors for SAD in patients with septic shock.[15] Conventional resuscitation processes based on hemodynamics and blood gas indicators ignore the importance of cerebral resuscitation. Near-infrared spectroscopy (NIRS) measuring regional cerebral oxygen saturation (rSO_2) has been proposed as a non-invasive system for monitoring regional circulation. Abnormal rSO_2 in severely ill patients is associated with the incidence of delirium.[16,17] For convenient non-invasive bedside cerebral monitoring, NIRS-based cerebrovascular reactivity parameters (tissue oxygen reactivity index [TOx] or tissue hemoglobin concentration reactivity index [THx]) can be obtained by analyzing the dynamic linear correlation coefficient between rSO_2 and MAP using ICM+ software (Cambridge Enterprise, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk).[18,19] This study aimed to apply cerebral autoregulation-directed optimal blood pressure management in patients with septic shock and analyze the impact of individualized blood pressure management on the incidence of delirium and prognosis in patients with septic shock.

Methods

Research participants

This randomized controlled trial was conducted in the general medical/surgical intensive care unit (ICU) at the Xiangya Hospital, Central South University. All procedures involved in this study were in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Xiangya Hospital, Central South University (Institutional Review Board number: 2018101082), and registered on ClinicalTrials.gov (NCT03879317). Informed consent was obtained from the legal representatives of all participating patients. Fifty-one patients with septic shock were enrolled between December 2020 and May 2022. Patients were considered eligible if they were (1) admitted to the ICU within 24 h of meeting the criteria for septic shock (sepsis 3.0[20]), (2) at the decompensation stage of shock requiring resuscitation, and (3) adults aged >18 years. The exclusion criteria were (1) patients who could not undergo NIRS monitoring due to anatomical factors, (2) patients with an underlying diagnosis of cognitive dysfunction, including dementia and coma, and (3) severe intracranial diseases, including intracerebral infection, cerebral hemorrhage, cerebral infarction, brain injury, intracranial tumor, and intracranial surgery. Patients were randomly assigned to the experimental group (n=26) or the control group (n=25) using a computer-generated random number table.

Experimental procedure

The treatment of patients with septic shock followed international guidelines[6] and was at the discretion of the attending intensive care physician. Sedation (target Richmond agitation-sedation scale [RASS] −3 to 0) and MV were administered as necessary. The blood pressure target of the control group was MAP ≥65 mmHg according to the guidelines.[6] Patients in the experimental group underwent NIRS (FORESIGHT monitor; CASMED, CAS Medical Systems Inc., Branford, Connecticut, USA) and invasive arterial pressure monitoring immediately after admission to the ICU. The ICM+ software was used to monitor and calculate TOx from the dynamic linear correlation coefficient between rSO_2 and MAP. The optimal MAP (MAPopt) was defined as the MAP where TOx reached its minimum value when plotted against MAP.[15] MAPopt is the value at which cerebrovascular reactivity is at its best. To quickly determine MAPopt, norepinephrine was titrated to increase the MAP within 1 h from 65 mmHg to 95 mmHg. The curves of left/right TOx *vs.* MAP were plotted. The MAP corresponding to the lowest TOx was recorded, and the higher values of the two sides were determined as the MAPopt. The patients' blood pressures in the experimental group were targeted within the range of MAPopt ±5 mmHg until shock resuscitation was completed (MAP >65 mmHg without vasoactive drugs, central venous pressure 8–12 mmHg, central venous oxygen saturation ≥70%, urine output >0.5 mL/(kg·h), and serum lactic acid [Lac] <2.0 mmol/L).

Data collection

The following data were collected upon admission to the ICU: the baseline data of patients (sex, age, basic disease, and disease type), the Glasgow coma scale score, the RASS scores, information on etiology of sepsis, the site of infection, hematological indicators (white blood cell count, neutrophil percentage, platelets), hepatic function (total bilirubin, direct bilirubin, alanine aminotransferase, and aspartate transaminase), kidney function (blood urea nitrogen and creatinine), arterial blood gases (oxygenation index [the partial pressure of oxygen/the fraction of inspired oxygen, PaO_2/FiO_2], Lac), indicators of infection (procalcitonin), and coagulation function (prothrombin

time, active partial thromboplastin, D-dimer). The severity of illness was assessed using the acute physiology and chronic health evaluation (APACHE) II and sepsis-related organ failure assessment (SOFA) scores; the types and doses of vasoactive, sedative, and analgesic drugs; and MV parameters. In the experimental group, the parameters of NIRS monitoring were recorded, including the maximum and minimum values of rSO_2, variation rate (calculated as $[rSO_2max–rSO_2min]/rSO_2max$), tissue oxygenation index (TOI), tissue hemoglobin concentration index (THI), and TOx during the first 6 h of monitoring. To screen for delirium, patients were assessed twice a day (8:00 AM and 8:00 PM) during their entire ICU stay using the confusion assessment method for the ICU.[10] For each sedated patient, the RASS score was assessed daily, and the presence of delirium assessed daily after waking. The duration of time spent on MV, length of ICU stay, length of hospital stay, and 28-day mortality were also recorded. The primary outcome was the incidence of delirium in the ICU, and the secondary outcomes were the length of ICU stay, duration of MV, number of organ dysfunctions, and 28-day mortality.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 statistical software (Armonk, NY: IBM Corp.). Normally distributed continuous were expressed as mean ± standard deviation. If the variances were equal, the independent samples *t*-test (Student's *t*-test) was used to compare groups; otherwise, the Mann–Whitney *U* test was used. Categorical data were analyzed using the chi-squared test. $P < 0.05$ was considered statistically significant. The risk factors for delirium and 28-day mortality were first analyzed by univariate regression analysis, and variables with $P < 0.20$ were included in multivariable regression analysis and adjusted for confounding factors. Logistic regression analysis results were recorded as odds ratio (OR) and 95% confidence intervals (CIs). The ability of rSO_2-related parameters to predict delirium and 28-day mortality was assessed using the area under the receiver operating characteristic curve (AUROC).

Results

Baseline characteristics

We included 51 patients with septic shock, including 39 male and 12 female, with a mean age of 57.0±14.9 years. The overall incidence of delirium was 40.1% (23/51). The 28-day mortality was 29.4% (15/51). The mean APACHE II score was 21.5±8.0, and the mean SOFA score was 10.4±4.4. The average length of ICU stay was (13.2±12.0) days, and the average length of MV was (8.1±9.4) days.

There were no significant differences in age, sex composition, APACHE II, SOFA, or Glasgow coma scale scores between the two groups. Patients in the control group had more basic cardiovascular diseases ($P=0.025$) and bloodstream infections ($P=0.025$). *Escherichia coli* infection was more common in the control group ($P=0.037$). The incidence of delirium was significantly lower in the experimental group than in the control group (30.8% [8/26] *vs.* 60.0% [15/25], respectively, $P=0.036$). There were no significant differences in the length of ICU stay, length

of MV, number of organ failures, incidence of acute kidney injury, or 28-day mortality between the two groups (Table 1).

Differences in clinical and biochemical indicators between groups

On the first day of admission, there were no significant differences in laboratory biochemical indicators between the groups. The MAP during the first 24 h in the ICU was significantly higher in the experimental group compared with the control group ([84.5±12.2]mmHg *vs.* [77.4±11.8]mmHg, $P=0.040$). This difference is because the experimental group used cerebral autoregulation-directed optimal blood pressure as the resuscitation target. At discharge, hemoglobin and albumin levels were significantly higher in the experimental group compared with the control group ($P=0.043$ and $P=0.046$, respectively). There were no significant differences in the other laboratory biochemical indicators between the groups at discharge (Tables 2 and 3).

Table 1
Patient demographics and clinical features.

Items	Control group (n=25)	Experimental group (n=26)	Total (n=51)	P-values
Age (years)	58.8±13.7	55.2±16.0	57.0±14.9	0.386
<40	3 (12.0)	3 (11.5)	6 (11.8)	0.959
40–59	7 (28)	12 (46.2)	19 (37.3)	0.180
60–79	13 (52.0)	10 (38.5)	23 (45.1)	0.331
≥80	12 (48.0)	6 (23.1)	18 (35.3)	0.063
Sex (Female/Male)	5/20	7/19	12/39	0.56
Medical history				
None	7 (28.0)	11 (42.3)	18 (35.2)	0.285
Cardiovascular diseases	11 (44.0)	4 (15.4)	15 (29.4)	0.025
Rheumaimmune systemic diseases	5 (20.0)	1 (3.8)	3 (5.9)	0.529
Digestive system diseases	4 (16.0)	6 (23.1)	10 (19.6)	0.525
Endocrine diseases	3 (12.0)	5 (19.2)	8 (15.9)	0.478
Tumor	2 (8.0)	2 (7.6)	5 (9.8)	0.605
Respiratory system diseases	2 (8.0)	1 (3.8)	3 (5.9)	0.529
Chronic renal insufficiency	0 (0.0)	1 (3.8)	1 (2.0)	0.322
Source of infection				
Pneumonia	22 (88.0)	18 (69.2)	40 (78.4)	0.103
Abdomen	8 (32.0)	11 (42.3)	19 (37.3)	0.447
Blood	11 (44.0)	4 (15.4)	15 (29.4)	0.025
Gastrointestinal	5 (20.0)	7 (26.9)	12 (23.5)	0.560
Urinary tract	4 (16.0)	4 (15.4)	8 (15.7)	0.952
Skin and soft tissue	2 (8.0)	2 (7.6)	4 (7.8)	0.967
Pathogenic culture				
Klebsiella pneumoniae	9 (36.0)	9 (34.6)	18 (35.2)	0.918
Acinetobacter baumanni	6 (24.0)	7 (26.9)	13 (25.4)	0.811
Escherichia coli	6 (24.0)	1 (3.8)	7 (13.7)	0.037
Pseudomonas aeruginosa	3 (12.0)	1 (3.8)	4 (7.8)	0.279
Burkholder Onion	2 (8.0)	0 (0.0)	2 (3.9)	0.141
Staphylococcus aureus	1 (4.0)	1 (3.8)	2 (3.9)	0.977
Fungus	8 (32.0)	4 (15.4)	12 (23.5)	0.162
Others	9 (36.0)	1 (3.8)	10 (19.6)	0.004
APACHE II	22.0±7.8	21.1±8.4	21.5±8.0	0.711
SOFA	10.7±4.5	10.1±4.5	10.4±4.4	0.631
GCS	9.1±5.3	10.7±4.9	9.9±5.1	0.273
Length of ICU stay (day)	16.5±15.1	10.1±7.1	13.2±12.0	0.062
Length of MV (day)	10.5±11.7	5.7±5.5	8.1±9.4	0.075
Number of organ failure	4.3±1.7	3.9±1.8	4.1±1.7	0.414
Incidence of delirium	15 (60.0)	8 (30.8)	23 (40.1)	0.036
Incidence of AKI	13 (52.0)	13 (50.0)	26 (51.0)	0.886
28-day mortality	8 (32.0)	7 (26.9)	15 (29.4)	0.691

Data are presented as *n* (%) and mean±standard deviation.
AKI: Acute kidney injury; APACHE: Acute physiology and chronic health evaluation; GCS: Glasgow coma scale; ICU: Intensive care unit; MV: Mechanical ventilation; SOFA: Sepsis-related organ failure assessment.

Table 2

Comparison of clinical characteristics and biochemical indicators on the first day between groups.

Items	Control group (*n*=25)	Experimental group (*n*=26)	Total (*n*=51)	*P*-values
MAP (mmHg)	77.4±11.8	84.5±12.2	81.0±12.4	0.040
Total 24 h intake (mL)	3115.4±1935.1	2936.3±1534.1	3019.3±1711.4	0.743
Total 24 h output (mL)	1980.0±1087.9	1965.0±1113.3	1971.9±1087.8	0.965
PH	7.4±0.1	7.4±0.1	7.4±0.1	0.422
PaO$_2$ (mmHg)	111.3±53.8	108.2±40.0	109.8±46.8	0.817
PaCO$_2$ (mmHg)	41.7±16.9	40.3±11.1	41.0±14.1	0.732
P/F	261.1±133.6	241.8±118.6	251.3±125.3	0.587
Lac (mmol/L)	3.7±4.2	3.0±2.2	3.3±3.3	0.445
ScvO$_2$ (%)	62.7±13.0	65.3±11.4	64.0±12.2	0.375
Pcv-aCO$_2$ (mmHg)	6.1±3.1	6.6±4.6	6.34±3.9	0.760
WBC (×10^9/L)	11.7±7.0	17.3±13.9	14.6±11.4	0.076
HB (g/L)	83.9±19.7	92.1±22.8	88.1±21.6	0.182
NE (%)	79.5±20.5	85.4±16.4	82.6±18.5	0.260
PCT (ng/mL)	31.5±43.2	32.4±33.0	32.0±37.9	0.969
CRP (mg/L)	147.7±72.9	163.6±112.1	155.8±94.3	0.539
ALB (g/L)	27.9±4.1	27.5±3.6	27.7±3.8	0.722
TBIL (μmol/L)	54.8±82.8	52.7±103.6	53.7±93.3	0.938
DBIL (μmol/L)	30.8±46.4	30.3±54.7	30.5±50.3	0.973
ALT (U/L)	79.5±155.7	127.3±292.9	104.4±236.1	0.480
AST (U/L)	112.4±112.9	178.6±298.9	146.8±229.6	0.301
BUN (mmol/L)	15.5±8.4	17.7±13.8	16.6±11.5	0.487
Cr (μmol/L)	184.3±97.4	205.3±195.5	195.2±155.1	0.638
Na (mmol/L)	144.9±8.8	143.9±6.9	144.4±7.8	0.660
K (mmol/L)	4.0±0.7	4.3±0.9	4.1±0.8	0.272
PLT (×10^9/L)	107.2±89.4	154.4±136.6	131.7±117.6	0.158
PT (s)	16.1±3.1	16.1±5.3	16.1±4.3	0.911
APTT (s)	47.8±16.2	44.5±7.4	46.1±12.5	0.393
FIB (g/L)	3.8±3.2	3.6±2.9	3.7±3.0	0.640
Norepinephrine (μg/(kg·min))	0.8±0.8	0.8±0.7	0.8±0.7	0.848
Midazolam (μg/(kg·min))	1.0±0.7	0.8±1.0	0.9±0.8	0.363
Remifentanil (μg/(kg·min))	0.04±0.3	0.03±0.03	0.03±0.03	0.181

Data are presented as mean ± standard deviation.
ALB: Albumin; ALT: Alanine aminotransferase; APTT: Active partial thromboplastin; AST: Aspartate transaminase; BUN: Blood urea nitrogen; Cr: Creatinine; CRP: C-reactive protein; DBIL: Direct bilirubin; FIB: Fibrinogen; HB: Hemoglobin; Lac: Serum lactic acid; MAP: Mean arterial pressure; NE: Neutrophil percentage; P/F: The partial pressure of oxygen /the fraction of inspired oxygen; PaCO$_2$: Partial pressure of carbon dioxide; PaO$_2$: Partial pressure of oxygen; PCT: Procalcitonin; Pcv-aCO$_2$: Central venous-to-arterial carbon dioxide difference; PLT: Platelets; PT: Prothrombin time; ScvO$_2$: Central venous oxygen saturation; TBIL: Total bilirubin; WBC: White blood cell.

Differences in the cerebral autoregulation-related indicators by delirium and survival status

In the experimental group, during the first 6 h of NIRS monitoring, there was no significant difference in the maximum rSO$_2$, minimum rSO$_2$, mean rSO$_2$, variation rates of rSO$_2$, THI, TOx, and MAPopt between patients with and without delirium. However, the actual MAP was much lower than the target MAP in patients with delirium, while patients without delirium maintained actual MAP within the range of MAPopt ±5 mmHg.

The mean rSO$_2$ (61.6±7.3 *vs.* 54.6±7.4, *P*=0.040) and min rSO$_2$ (57.2±8.7 *vs.* 48.6±9.5, *P*=0.038) were significantly higher among patients who survived compared to patients who died. There was no significant difference in the maximum rSO$_2$, variation rate of rSO$_2$, mean THI, TOx, MAP, or MAPopt by survival status (Table 4).

Table 3

Comparison of clinical characteristics and biochemical indicators at discharge between groups.

Items	Control group (*n*=25)	Experimental group (*n*=26)	Total (*n*=51)	*P*-values
MAP (mmHg)	73.7±17.9	74.2±27.6	74.0±23.1	0.943
PH	7.4±0.2	7.3±0.2	7.4±0.2	0.672
PaO$_2$ (mmHg)	110.2±34.6	101.2±41.2	105.7±37.9	0.409
PaCO$_2$ (mmHg)	39.0±9.7	42.1±13.0	40.6±11.4	0.346
P/F	273.3±130.9	230.0±133.1	251.2±132.5	0.247
Lac (mmol/L)	5.2±5.6	4.9±5.5	5.1±5.5	0.849
ScvO$_2$ (%)	54.4±10.8	58.1±12.5	56.2±11.7	0.498
Pcv-aCO$_2$ (mmHg)	10.0±7.2	8.80±5.18	9.4±6.2	0.332
WBC (×10^9/L)	13.5±9.4	15.9±14.8	14.7±12.3	0.507
HB (g/L)	74.6±16.6	86.6±22.7	80.6±20.6	0.043
NE (%)	74.7±24.2	80.4±19.6	77.6±22.0	0.552
PCT (ng/mL)	21.8±29.3	28.3±32.9	25.1±31.1	0.646
CRP (mg/L)	120.3±74.7	128.0±43.5	124.3±60.3	0.658
ALB (g/L)	29.8±4.8	31.9±3.6	30.8±4.3	0.046
TBIL (μmol/L)	78.4±97.4	97.1±148.3	87.9±125.0	0.625
DBIL (μmol/L)	44.8±51.1	57.0±88.6	51.1±72.2	0.549
ALT (U/L)	395.9±1001.7	125.3±127.3	258.0±713.0	0.175
AST (U/L)	1009.0±2092.6	405.0±696.8	701.1±1561.3	0.166
BUN (mmol/L)	19.5±12.5	14.7±9.9	17.0±11.4	0.141
Cr (μmol/L)	187.0±109.6	150.4±101.5	168.3±106.1	0.230
Na (mmol/L)	145.0±8.6	144.6±8.1	144.8±8.3	0.857
K (mmol/L)	4.2±0.8	4.2±0.8	4.2±0.8	0.700
PLT (×10^9/L)	118.2±117.8	139.7±129.8	128.9±123.1	0.552
PT (s)	20.3±10.5	16.5±5.8	18.4±8.6	0.096
APTT (s)	54.6±19.9	45.5±12.0	50.0±16.9	0.050
FIB (g/L)	3.7±3.1	3.2±1.8	3.4±2.5	0.608

Data are presented as mean ± standard deviation.
ALB: Albumin; ALT: Alanine aminotransferase; APTT: Active partial thromboplastin; AST: Aspartate transaminase; BUN: Blood urea nitrogen; Cr: Creatinine; CRP: C-reactive protein; DBIL: Direct bilirubin; FIB: Fibrinogen; HB: Hemoglobin; Lac: Serum lactic acid; MAP: Mean arterial pressure; NE: Neutrophil percentage; P/F: The partial pressure of oxygen /the fraction of inspired oxygen; PaCO$_2$: Partial Pressure of Carbon Dioxide; PaO$_2$: Partial pressure of oxygen; PCT: Procalcitonin; Pcv-aCO$_2$: Central venous-to-arterial carbon dioxide difference; PLT: Platelets; PT: Prothrombin time; ScvO$_2$: Central venous oxygen saturation; TBIL: Total bilirubin; WBC: White blood cell.

Table 4

Comparison of cerebral autoregulation-related indicators between patients by delirium and survival status.

Items	Delirium	Without delirium	*P*-values	Death	Survival	*P*-values
rSO$_2$max	66.1±11.7	64.6±7.0	0.690	61.3±6.9	66.5±8.7	0.173
rSO$_2$min	56.5±6.1	54.1±10.8	0.569	48.6±9.5	57.2±8.7	0.038
rSO$_2$mean	60.1±7.6	59.6±8.1	0.882	54.6±7.4	61.6±7.3	0.040
rSO$_2$ variation rate	0.1±0.1	0.2±0.2	0.615	0.2±0.2	0.1±0.1	0.281
THI	0.8±0.2	0.8±0.3	0.699	0.8±0.1	0.8±0.3	0.463
TOx	0.2±0.2	0.1±0.2	0.303	0.2±0.1	0.05±0.2	0.126
MAP	67.9±16.6	87.0±22.0	0.038	74.7±14.2	83.5±24.2	0.378
MAPopt	84.4±13.1	90.1±10.9	0.257	89.3±8.3	88.0±12.9	0.809

Data are presented as mean ± standard deviation.
MAP: Mean arterial pressure; MAPopt: The optimal MAP; rSO$_2$: Regional cerebral oxygen saturation; THI: Tissue hemoglobin concentration index; TOx: Tissue oxygen reactivity index.

Risk factors for delirium and 28-day mortality

The logistic regression analysis identified cerebral autoregulation-directed optimal blood pressure (OR=0.090, 95% CI=0.009 to 0.923, *P*=0.043) and length of ICU stay (OR=1.473, 95% CI=1.093 to 1.985, *P*=0.011) as the risk factors for delirium. The AUROCs for cerebral autoregulation-directed optimal blood pressure and length of ICU stay were
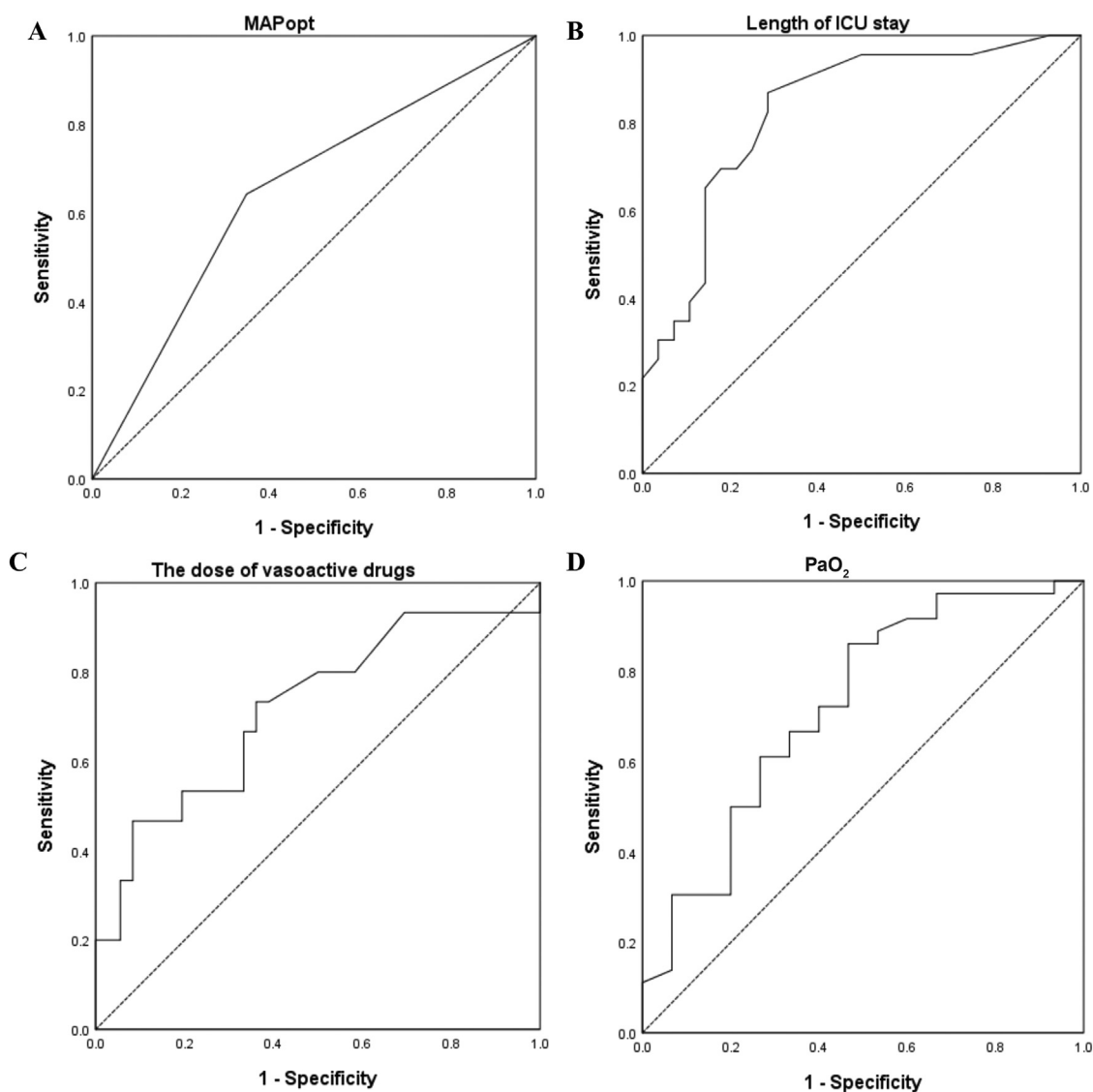
Figure 1. The AUROC curves for predicting the incidence of delirium or 28-day mortality. A: The AUROC for the use of MAPopt was 0.648 when predicting the incidence of delirium. B: The AUROC for the length of ICU stay was 0.830 when predicting the incidence of delirium. C: The AUROC curve for the dose of vasoactive drugs was 0.719 when predicting 28-day mortality. D: The AUROC for PaO_2 was 0.720 when predicting 28-day mortality. AUROC: Area under the receiver operating characteristic curve; ICU: Intensive care unit; MAPopt: Optimal mean arterial pressure; PaO_2: Partial pressure of oxygen.

0.648 and 0.830, respectively, when predicting the incidence of delirium.

The risk factors for 28-day mortality included the dose of vasoactive drugs (OR=8.445, 95% CI=1.260 to 56.576, P=0.028) and PaO_2 (OR=0.958, 95% CI=0.921 to 0.996, P=0.032). In predicting 28-day mortality, the AUROC for the dose of vasoactive drugs was 0.719 and that for PaO_2 was 0.720 (Table 5 and Figure 1).

Discussion

Sepsis and septic shock are characterized by acute onset, rapid development, and high mortality. SAD is a common clinical manifestation that can occur at any stage of sepsis. In the present study, the incidence of delirium in patients with septic shock was 40.1%. The incidence of delirium in patients with sepsis can be as high as 70%.[12] Therefore, more attention should be paid to SAD in the clinical practice. The conventional sep-

Table 5
Risk factors for delirium and 28-day mortality.

Item	OR	P-value	95% CI
Risk factors for delirium			
Whether using cerebral autoregulation-directed optimal blood pressure	0.090	0.043	0.009 to 0.923
Length of ICU stay	1.473	0.011	1.093 to 1.985
Risk factors of 28-day mortality			
Dose of vasoactive drugs	8.445	0.028	1.260 to 56.576
PaO_2	0.958	0.032	0.921 to 0.996

CI: Confidence interval; ICU: Intensive care unit; OR: Odds ratio; PaO_2: Partial pressure of oxygen.

tic shock resuscitation target of MAP ≥65 mmHg recommended by existing guidelines is not suitable for all patients, particularly those with basic hypertension, which may lead to insufficient cerebral perfusion. Cerebral microcirculation disorders and cerebral perfusion insufficiency are involved in the patho-

genesis of SAD.[14,15] Patients in the late stage of sepsis have impaired cerebral autoregulatory function,[21] which is closely related to the occurrence of delirium.[15] Therefore, optimal cerebral pressure management may help improve the prognosis of patients with septic shock.

Cerebral autoregulation is a function that maintains constant cerebral blood flow (CBF) despite changes in MAP or cerebral perfusion pressure (CPP). MAPopt is associated with improved outcomes for patients.[22,23] Hence, a new concept based on individualized and CPPopt-targeted management has been developed,[23,24] which is dependent on real-time CBF autoregulation monitoring and calculates the correlation coefficient with arterial blood pressure to identify the CPPopt value. A previous study suggested that management of CPP within the range of CPPopt $\pm$5 mmHg is associated with better outcomes in patients with brain injury.[24]

Pressure reactivity index (PRx) is the most commonly used method for monitoring dynamic cerebrovascular reactivity index.[21,25] A positive PRx indicates a positive correlation between intracranial pressure (ICP) and arterial blood pressure and is associated with both mortality and poor neurological recovery in traumatic brain injury.[21,25,26] However, PRx assessment requires invasive ICP monitoring, which limits its clinical application. Alternatively, in the absence of invasive ICP monitoring to determine CPP, continuous autoregulation monitoring can be accomplished using non-invasive cerebral monitoring, such as the continuous correlation between the transcranial Doppler-measured CBF velocity of the middle cerebral artery and MAP (termed Mx).[21,23,25,27-34] Mx is a validated index of cerebral autoregulation; however, it is impractical for long-term monitoring and requires system training, and the results are operator-dependent. NIRS measurements are an alternative method for real-time autoregulation monitoring in the form of a TOI.[35] Compared to transcranial Doppler, NIRS sensors are easy to attach to the forehead and do not require frequent calibration, making this method more suitable for long-term monitoring. NIRS uses non-invasive technology to compare different absorption spectra of oxyhemoglobin and deoxyhemoglobin in relation to the relative total hemoglobin.[21] A continuous correlation between the relative total hemoglobin and arterial blood pressure (TOx or THx) accurately detected the lower limit of autoregulation and functioned as a PRx.[18,19] Therefore, in the present study, we adopted non-invasive NIRS monitoring to calculate the dynamic changes in rSO_2 and MAP using the ICM$^+$ software in the early stage of septic shock; MAPopt was determined by the lowest TOx, which indicated the best cerebrovascular autoregulation in the range of MAP regulation.

The present study found that cerebral autoregulation-directed MAP management in patients with septic shock reduced the incidence of delirium (60.0% vs. 30.8%; P=0.036). In the experimental group, patients without delirium maintained actual MAP within the range of MAPopt $\pm$5 mmHg, while the actual MAP was much lower than the target MAP in patients with delirium. A previous study also found that using intra-operative cerebral autoregulation monitoring to optimize the MAP was better than the individual patient's lower limit of autoregulation during cardiopulmonary bypass surgery, reducing the incidence of post-operation delirium.[36] Our study indicates that cerebral autoregulation-directed MAPopt is a poten-

tial individualized MAP-management strategy for septic shock resuscitation, which deserves further study for other types of shock.

Previous studies have reported many potential risk factors for delirium, including age, preexisting cognitive impairment, psychiatric disorders, cerebrovascular disease, end-stage renal failure, low albumin levels, and intra-operative blood transfusion.[37] In our study, the use of cerebral autoregulation-directed optimal blood pressure and length of ICU stay were risk factors for delirium during septic shock. Low diastolic blood pressure is independently associated with the development of delirium in patients experiencing shock.[38] The length of ICU stay was also significantly associated with postoperative delirium in patients undergoing esophagectomy.[39] These results indicate that maintaining appropriate blood pressure and reducing the length of ICU stay are important factors that require attention in clinical practice.

In the present study, cerebral autoregulation-directed MAP management in patients with septic shock did not reduce 28-day mortality (32.0% vs. 26.9%, P=0.691). However, the rSO_2 was significantly higher in survivors than in non-survivors. A previous study also reported that non-survivors of pediatric cardiac surgery had significantly lower cerebral saturation than survivors.[40] The risk factors for 28-day mortality were the dose of vasoactive drugs and PaO_2. Norepinephrine is a vasopressor recommended for maintaining MAP in patients with septic shock.[6] Early administration of norepinephrine is beneficial for restoring organ perfusion, increasing cardiac output, improving microcirculation, and preventing complications related to fluid overload in patients with septic shock. However, high doses of norepinephrine may have deleterious consequences, including cardiovascular damage, oxidative stress, and altered immune regulation.[41] In a retrospective study of 324 patients with septic shock, the mean mortality rate was 48%, but patients receiving norepinephrine above 1 μg/(kg·min) had a mortality rate of 90%.[42] Every 10 μg/min increase in norepinephrine equivalent dose at the start of vasopressin was associated with a 20.7% increase in in-hospital mortality.[43] Thus, vasoactive drug dose is associated with mortality due to septic shock. Sepsis is also the leading indirect cause of acute respiratory distress syndrome, which leads to higher mortality of patients.[44] The decrease in PaO_2 may result from insufficient blood perfusion or lung injury, which is unfavorable for tissue oxygen supply. Therefore, a low PaO_2 may also be associated with mortality due to septic shock.

The present study had some limitations. First, this was a single-center study of only 51 patients with septic shock. Therefore, a relatively small sample size may have affected our results. Second, the NIRS monitoring value may be affected by external factors, such as the electrode placement site, body position, local tissue edema, and differences in the distribution ratio of arteries and veins. Third, although we intended to maintain the MAP within MAPopt $\pm$5 mmHg in the experimental group, several patients did not always maintain the MAP in this range because of the fluctuation of blood pressure. Fourth, we only performed cerebral autoregulation-directed optimal blood pressure management in the early stage of septic shock, but did not maintain MAP management and adjust the MAPopt target throughout the treatment period.

Conclusions

Using non-invasive NIRS monitoring and ICM$^+$ software to determine cerebral autoregulation-directed optimal blood pressure at the early stage of resuscitation may reduce the risk of delirium in patients with septic shock.

Author Contributions

Qianyi Peng: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Writing – original draft. **Xia Liu:** Data curation, Formal analysis, Project administration, Writing – original draft. **Meilin Ai:** Project administration. **Li Huang:** Project administration. **Li Li:** Project administration. **Wei Liu:** Project administration. **Chunguang Zhao:** Project administration. **Chenghuan Hu:** Project administration. **Lina Zhang:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Ethical Statement

All procedures involved in this study were in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Xiangya Hospital, Central South University (Institutional Review Board number: 2018101082).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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