Is impaired cerebrovascular autoregulation associated with outcome in patients admitted to the ICU with early septic shock?

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ABSTRACT

Objective: To investigate the correlation between early changes in cerebrovascular autoregulation (CVAR) and neurological outcome and mortality in patients admitted to the intensive care unit with septic shock.

Design, setting and participants: A prospective observational study in a tertiary, university-affiliated ICU, of 28 patients with septic shock (median age, 66 years; interquartile range [IQR], 56–74 years), with a median APACHE III score of 86 (IQR, 55–119).

Main outcome measures: We used the correlation in time between cerebral tissue oxygenation (measured with near infrared spectroscopy) and mean arterial pressure to determine the tissue oxygenation reactivity index (TOx) as a measure of CVAR. Low TOx represents intact CVAR and high TOx represents impaired CVAR. We performed the measurements in the first 3 days after admission to the ICU. Survival and neurological outcomes, measured using the modified Rankin Scale and the Cerebral Performance Category scale, were censored 3 months later.

Results: All survivors of septic shock had a good neurological outcome. The TOx for Days 1–3 was higher ($P < 0.001$) in non-survivors (median, 0.04 [IQR, 0.12–0.24]) compared with survivors (median, –0.02 [IQR, –0.13 to 0.05]). The TOx was independently associated with survival at 3 months (odds ratio, 0.13 [95% CI, 0.01–0.69]; $P < 0.05$) using logistic regression analysis.

Conclusions: CVAR is impaired early in septic shock and is independently associated with mortality at 3-month follow-up. Information based on bedside monitoring of CVAR in the ICU could form a valuable adjunct to guide haemodynamic optimisation in patients with septic shock.

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Ischaemic cerebral lesions are a major pathological finding in patients dying from septic shock,[1] and sepsis-associated encephalopathy is thought to reflect cerebral hypoperfusion.[2] The current understanding of cerebral perfusion in sepsis is incomplete, and it is thought to involve complex pathophysiological inflammatory, immunological and metabolic mechanisms, whose effects on brain perfusion remain unclear.

Cerebrovascular autoregulation (CVAR) maintains cerebral oxygen delivery while arterial pressure or cardiac output changes. Any compromise to CVAR exposes the brain to the risk of inadequate perfusion, particularly hypoperfusion when there is arterial hypotension.

Studies of CVAR in patients with sepsis have generated equivocal results. Evidence of compromised CVAR using transcranial Doppler ultrasound to assess blood flow velocity has been shown during endotoxinaemia[3] in patients with sepsis,[4] and in most patients with severe sepsis or septic shock.[5,6] Other studies have reported maintained or enhanced CVAR in patients with sepsis[7] or endotoxinaemia[8,9] and normal-to-low arterial CO_2 levels, although cerebral blood flow might still be reduced.

Near-infrared spectroscopy (NIRS) can be used to monitor low-frequency fluctuations of cerebral tissue oxygenation ($Scto_2$), which can be used as a surrogate of cerebral blood flow slow waves. NIRS can therefore be used to assess CVAR[10,11] in patients with sepsis.[12] An index of dynamic autoregulation (the tissue oxygenation reactivity index [TOx]) is derived by correlating changes in $Scto_2$ and blood pressure across a range of arterial pressures.

Our aim was to consecutively assess TOx in patients admitted to the intensive care unit for septic shock, in relation to their neurological outcome and survival at 3 months. We hypothesised that patients who had poor neurological outcomes or death would have had impaired CVAR.

Methods

Our prospective observational study was approved by the South Western Sydney Local Health District Human Research and Ethics Committee (HREC/13/LPOOL/455). All patients with septic shock[13] admitted to the Liverpool Hospital ICU between February and July 2014 were screened within 24 hours of admission for eligibility to be included in our study. Patients were excluded if they were younger than 18 years, had anatomical features that precluded the use of NIRS, had an intracranial source of sepsis, had a significant previous cerebral injury or death was deemed imminent. Consent was obtained from a senior next of kin and from the patient if they were subsequently able to consent.

All patients were sedated, mechanically ventilated and managed at the discretion of the treating ICU team as per current guidelines,[14] including titration of vasopressor

Table 1. Baseline characteristics of patients admitted to the intensive care unit with sepsis

Patient no.	Sex	Age, years	Source of sepsis	APACHE III score	SAPS II score	Cardiovascular comorbidity*	Cerebrovascular disease†	Medications‡
1	M	65	Pneumonia	52	37	Yes	No	Asp
2	M	58	Abdominal	74	45	Yes	Yes	Nil
3	F	69	Abdominal	138	68	Yes	No	Asp, DU, OAH
4	M	71	Suspected renal/UTI	136	77	Yes	Yes	Asp, ARB, OAH
5	M	73	Pneumonia	120	78	Yes	No	W
6	M	78	Suspected renal/UTI	141	76	Yes	Yes	Asp, ACEI, CCB, OAH
7	M	87	Suspected renal/UTI	115	73	Yes	No	Asp
8	F	33	Suspected pneumonia	56	36	No	No	Nil
9	F	83	Abdominal	88	53	Yes	No	ACEI, CCB, OAH
10	F	43	Abdominal	85	50	No	No	Nil
11	M	64	Pneumonia	76	36	No	No	Nil
12	F	30	Pneumonia	44	27	No	No	Nil
13	M	74	Abdominal	41	43	Yes	No	Asp, ARB, CCB, α, β
14	F	63	Pneumonia	93	69	Yes	No	ARB, CCB, DU, OAH
15	M	75	Pneumonia	47	29	Yes	No	ARB, CS, β
16	F	85	Abdominal	107	65	Yes	No	Nil
17	F	56	Suspected pneumonia	86	55	No	No	Nil
18	F	71	Renal/UTI	80	44	Yes	No	Asp, ACEI, CCB, OAH
19	M	66	Pneumonia	86	55	Yes	No	Chem, W, α
20	F	33	Abdominal	54	30	No	No	Nil
21	M	66	Renal/UTI	157	97	Yes	No	CCB, DU, OAH
22	M	71	Pneumonia	76	52	Yes	No	CS
23	M	79	Soft tissue	134	65	Yes	No	Asp, ACEI, DU, α
24	M	46	Pneumonia	66	45	No	No	Nil
25	M	63	Abdominal	87	44	Yes	Yes	ACEI, Stat, CCB
26	F	57	Pneumonia	52	40	Yes	No	Nil
27	F	61	Pneumonia	139	75	Yes	Yes	Asp, ARB, CCB, CS
28	F	53	Pneumonia	52	47	Yes	No	OAH

APACHE = Acute Physiology and Chronic Health Evaluation. SAPS = Simplified Acute Physiology Score. UTI = urinary tract infection. * History of hyperlipidaemia, hypertension, atrial fibrillation, ischaemic heart disease, congestive heart failure, peripheral vascular disease, rheumatic heart disease or previous cardiac arrest. † Previous subarachnoid haemorrhage, subdural haematoma, stroke or transient ischaemic attack, or dementia. ‡ Asp = aspirin. DU = diuretic. OAH = oral antihyperglycaemic. ARB = angiotensin receptor blocker. W = warfarin. ACEI = angiotensin-converting enzyme inhibitor. CCB = calcium channel blocker. α = alpha-blocker. β = beta-blocker. CS = corticosteroid. Chem = chemotherapy. Stat = statin.

support to a mean arterial pressure (MAP) of 70–90 mmHg. Clinicians were blinded to the NIRS-derived measurements.

Measurements and calculations

Left and right frontal optodes connected to the Fore-Sight MC-2030 Universal Cerebral Oximeter (CAS Medical) were used to monitor Sct_{O_2} at a rate of 0.5 Hz. The Fore-Sight optodes were well shielded from ambient light in a black rubber assembly and were fixed to the skin with gauze wrapped around the patient's head. Radial MAP was monitored using a 20G cannula (Vygon) at 200 Hz with an IntelliVue MP70 monitor (Philips Healthcare), along with heart rate (HR) and arterial partial pressure of carbon dioxide ($Paco_2$) (ABL 800, Radiometer). We used ICM+ data acquisition and analysis software (University of Cambridge) to record and process all data. We made daily recordings in patients for the first 3 days after admission to the ICU, with a median duration of 85 minutes per recording (interquartile range [IQR], 66–98 minutes).

We used a 10-second moving average of the raw signals to derive the TOx, through a 5-minute moving Pearson correlation between slow fluctuations of Sct_{O_2} and the MAP that was updated every 30 seconds. The dimensionless nature of TOx is conducive to interpatient comparisons. A positive correlation in the time domain between Sct_{O_2} and MAP (TOx > 0) represented pressure-passive changes in cerebral

Table 2. Cardiorespiratory variables; GCS, SOFA and RASS scores; and vasopressor and analgosedative requirements for the first 3 days in the ICU

Variable	Group	Median (IQR) on Day 1, *n* = 28	Median (IQR) on Day 2, *n* = 23	Median (IQR) on Day 3, *n* = 22	*P* (Day 1, Day 2, Day 3, Days 1–3)
MAP, mmHg	Non-survivors	71 (69–75)	75 (70–84)	79 (74–87)	0.22, 0.94, 0.15, 0.04**
	Survivors	77 (70–83)	74 (72–81)	76 (71–79)	
HR, beats/min	Non-survivors	99 (85–108)	86 (79–101)	87 (80–101)	0.001,** 0.23, 0.34, 0.33
	Survivors	76 (73–79)*	101 (80–116)	95 (86–104)	
GCS score	Non-survivors	4 (3–9)	9 (3–10)	10 (6–11)	0.19, 0.54, 0.98, 0.26
	Survivors	9 (6–10)	10 (6–11)	10 (6–13)	
SOFA score	Non-survivors	14 (10–15)	12 (9–13)	9 (8–15)	0.50, 0.86, 0.52, 0.06
	Survivors	11 (8–14)	9 (8–11)	9 (7–12)	
Noradrenaline per day, mg	Non-survivors	11 (4.2–35)	8.5 (1.9–31)	1.9 (1.1–12)	0.66, 0.29, 0.96, 0.03**
	Survivors	15 (6.7–53)	12 (6.1–26)	1.5 (1.1–14)	
Fentanyl per day, mg	Non-survivors	0.66 (0.38–1.0)	0.77 (0.31–1.2)	0.43 (0.30–0.81)	0.02,** 0.98, 0.03,** 0.09
	Survivors	0.98 (0.75–1.5)*	0.68 (0.37–1.2)	1.0 (0.53–1.6)*	
Propofol per day, g	Non-survivors	0.74 (0.42–1.5)	1.2 (0.46–2.1)	0.60 (0.31–0.95)	0.02,** 0.31, 0.05, 0.04**
	Survivors	1.8 (0.94–2.5)*	2.4 (1.0–2.9)	2.0 (0.71–2.4)	
RASS score	Non-survivors	–4 (–4 to –1)	–1 (–5 to –1)	–1 (–4 to 0)	0.49, 0.47, 0.47, 0.18
	Survivors	–2 (–4.5 to –1)	–1 (–3.5 to –0.25)	–1.5 (–3.5 to –0.25)	
$Paco_2$, mmHg	Non-survivors	39 (32–44)	36 (33–40)	36 (33–38)	0.66, 0.29, 0.01,** 0.50
	Survivors	40 (36–45)	38 (36–40)	43 (37–45)*	
Lactate, mmol/L	Non-survivors	2.2 (1.3–4.1)	1.8 (1.2–3.6)	1.8 (1.1–3.1)	0.09, 0.11, 0.03,** 0.67
	Survivors	1.2 (0.86–3.1)	1.0 (0.75–2.1)	1.1 (0.75–1.5)*	

GCS = Glasgow Coma Scale. SOFA = Sequential Organ Failure Assessment. RASS = Richmond Agitation–Sedation Scale. ICU = intensive care unit. IQR = interquartile range. *n* = number of patients remaining alive and in the study. MAP = mean arterial pressure. HR = heart rate. * Non-survivors compared with survivors. ** Different at time compared for all patients.

oxygenation and thus indicated impaired CVAR. Inversely, a lack of or negative correlation (TOx ≤ 0) indicated intact CVAR.[11] The TOx values were categorised in MAP "bins" of 5 mmHg, as an indication of the prevailing autoregulatory capacity for each level of blood pressure, and an automated curve-fitting method was applied.[15] The least TOx (the optimum autoregulatory capacity) on the fitted curve was recorded as opt-TOx, along with the corresponding MAP (MAP_{OPT}), as calculated by the ICM+ software.[16]

Patient outcomes

The severity of illness was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) III score, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) score. Sedation was monitored using the Richmond Agitation–Sedation Scale (RASS), aiming for a score of –3 to 0. Neurological status, assessed using the modified Rankin Scale (mRS) and the Cerebral Performance Category (CPC) scale, and mortality were censored at 3 months after admission to the ICU. We assessed outcome as the composite of death and poor neurological function (mRS, 4–6; CPC, 3–5). Two of us (J B and P P) performed all neurological follow-ups and had access to names and birth dates but no specific results on CVAR at the time of assessment.

Statistical analyses

We tested data distribution using the Shapiro–Wilk test, and report results as means and standard deviations (SDs), medians and IQRs, or absolute values and percentages for each day, and averages over 3 days, as appropriate. The mean of left and right Sct_{O_2}, TOx, opt-TOx and MAP_{OPT} were analysed and are reported as the daily group average results, split by outcome. We compared continuous variables using the unpaired Student *t* test or the Mann–Whitney *U* test, and report differences including 95% confidence intervals. We analysed changes over time within one group using the Kruskal–Wallis test. The receiver operating characteristic (ROC) against outcome for TOx is expressed by the area under the curve (AUC) with its 95% CI and the criterion for best sensitivity and specificity (the Youden *J* statistic). We used the criterion for TOx to dichotomise opt-TOx into

impaired or intact CVAR, and calculated the odds ratio (OR) and its 95% CI for survival using the Fisher exact test. Variables that showed a difference in bivariate analysis between non-survivors and survivors were entered into a logistic regression model (entered if $P < 0.05$, removed if $P > 0.1$), using the values from Days 1–3 to predict outcome, and are reported as ORs and 95% CIs. A $P < 0.05$ was considered significant. We used SPSS, version 22 (IBM) for all statistical analyses.

Results

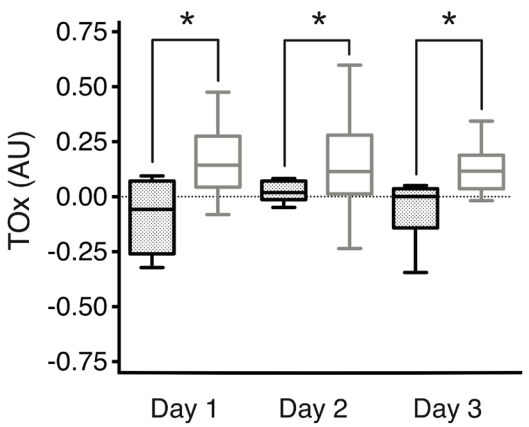
Patient characteristics and outcomes

Twenty-eight patients, including 15 men, were included in the study (median age, 66 years [IQR, 56–74 years]) (Table 1). Cardiorespiratory variables, vasopressor requirements, sedative and analgesic drugs, and RASS scores of the included patients are listed in Table 2. Adrenaline, dobutamine, vasopressin or milrinone was used at some time during the first 3 days in six non-surviving patients (data not shown).

HR was higher in non-survivors on Day 1. MAP and vasopressor support were not different between groups, although MAP increased and vasopressor requirements decreased over time. Less sedatives and analgesics were administered to non-survivors on Day 1. Lactate was lower and $Paco_2$ higher in survivors on Day 3.

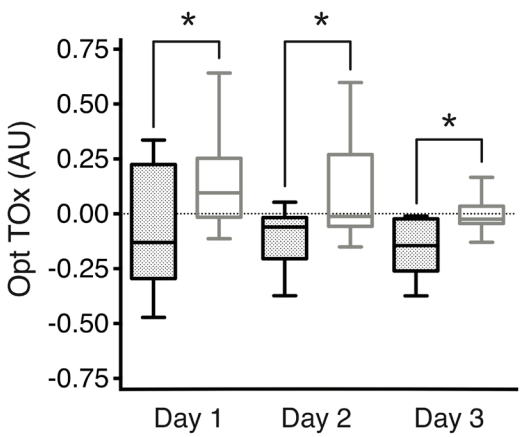
Six patients (21%) died within the first 3 days in the ICU and another 12 patients died after discharge from the ICU, leading to an overall mortality at 3 months of 64%. All survivors had good neurological outcomes when followed up at 3 months (median mRS score, 1 [IQR, 0–2]; median CPC score, 1 [IQR, 1–2]), with only one patient reporting moderate disability (mRS, 3).

Figure 1. Tissue oxygenation reactivity index (TOx) in survivors and non-survivors at 3-month follow-up, for Days 1, 2 and 3 in the intensive care unit



Black line, shaded boxes = survivors. Light grey line, open boxes = non-survivors. Boxes show median (line in boxes), interquartile range (box limits) and minimum and maximum (whiskers). * $P < 0.05$, using Mann–Whitney *U* test comparing survivors with non-survivors.

Figure 2. Optimal tissue oxygenation reactivity index (opt-TOx) in survivors and non-survivors at 3-month follow-up, for Days 1, 2 and 3 in the intensive care unit



Black line, shaded boxes = survivors. Light grey line, open boxes = non-survivors. Boxes show median (line inside boxes), interquartile range (box limits) and minimum and maximum (whiskers). * $P < 0.05$, using Mann–Whitney *U* test comparing survivors with non-survivors.

Changes in TOx

The TOx was consistently lower in survivors compared with non-survivors on Day 1 (median difference in TOx, 0.20 [IQR, 0.11–0.40]; $P = 0.0015$), on Day 2 (median difference, 0.096 [IQR, 0.006–0.26]; $P = 0.035$) and on Day 3 (median difference, 0.12 [IQR, 0.07–0.29]; $P = 0.0022$) (Figure 1). Although TOx improved in four survivors and eight non-survivors over the first 3 days, this change did not reach significance ($P = 0.35$ and $P = 0.81$, respectively). The ROC analysis for TOx v outcome generated an AUC of 0.84 (IQR, 0.74–0.92; $P < 0.0001$), with the optimal criterion being TOx < 0.09 for a favourable outcome.

Changes in opt-TOx

The opt-TOx was consistently lower in survivors compared with non-survivors on Day 1 (median difference, 0.23 [IQR, 0.01–0.43]; $P = 0.040$), on Day 2 (median difference, 0.05 [IQR, –0.005 to 0.34]; $P = 0.046$) and on Day 3 (median difference, 0.12 [IQR, 0.007–0.25]; $P = 0.030$) (Figure 2). The opt-TOx did not change over time within the group of survivors ($P = 0.88$), but decreased in non-survivors ($P = 0.04$). The MAP_{OPT} was not different in survivors compared with non-survivors. The median MAP_{OPT} values for survivors v non-survivors were: Day 1, 76 mmHg (IQR, 66–82 mmHg) v 72 mmHg (IQR, 67–78 mmHg), $P = 0.41$;

Day 2, 73 mmHg (IQR, 63–88 mmHg) v 76 mmHg (IQR, 72–85 mmHg), $P = 0.53$; and Day 3, 78 mmHg (IQR, 70–97 mmHg) v 82 mmHg (IQR, 74–92 mmHg), $P = 0.71$. With ICM+ software, we were able to calculate an opt- TOx and MAP_{OPT} for all patients on Day 1, but these variables could not be calculated in four non-survivors and one survivor for Days 2 and 3. The opt-TOx was dichotomised to represent intact (opt-TOx < 0.09) or impaired (opt-TOx ≥ 0.09) CVAR. The dichotomised opt-TOx was significantly different ($P < 0.05$) between survivors (seven intact; three impaired) and non-survivors (five intact; 13 impaired) on Day 1, resulting in an OR for survival of 6.1 (IQR, 1.1–33). The dichotomised opt-TOx was not significantly different on Day 3, because two patients who ultimately did not survive regained an intact CVAR ($P = 0.19$).

Associations with outcome

Seven predictor variables (HR, MAP, $Paco_2$, lactate level, APACHE III score, $Scto_2$ and TOx) were entered into the multivariate logistic regression that was significant ($\chi^2 = 26.7$; $P < 0.0001$) and explained 87% of the variance in outcome and correctly classified 93% of cases. Only TOx was significant among the predictor variables, and an increased TOx was associated with a reduced likelihood of survival (OR, 0.13 [IQR, 0.01–0.69]; $P = 0.035$).

Discussion

Our study of patients admitted to the ICU with early septic shock showed an association between CVAR capacity and the composite outcome of survival and neurological status at 3-month follow-up. All survivors had a favourable neurological outcome (mRs range, 0–3; CPC range, 1–2) and had better maintained TOx and opt-TOx compared with non-survivors. The TOx measured over the first 3 days in the ICU was independently associated with outcome in a multivariate logistic regression.

The high mortality in our cohort of patients with septic shock meant that the separation in the composite outcome variable was driven by deaths, rather than by neurological status, particularly since all surviving patients had good function at the 3-month follow-up. The mortality was higher compared with previous studies on CVAR in patients with sepsis.[4,5]

The TOx results were consistent with the most severe impairment of CVAR observed in non-survivors of septic shock, but survivors still showed reduced CVAR (comparable to levels of CVAR seen in comatose survivors of cardiac arrest).[17] Our study provides strong support that CVAR is compromised in early septic shock, which is in agreement with previous reports.[4-6,18] CVAR also remained impaired over the first 3 days in the ICU with ongoing treatment of sepsis, suggesting that the risk of cerebral insults as a consequence of hypoperfusion extends over a prolonged period of time.

Hypercarbia and arterial hypotension (which are known to impair CVAR[6,12]) were absent in both groups. Sedation with propofol may impair CVAR,[19] but the doses were not different between groups. Other mechanisms to explain impaired CVAR include endothelial activation with altered vascular tone and microcirculatory dysfunction.[20]

The importance of TOx in monitoring impaired CVAR is further underlined by its independent association with outcome in the multivariate regression analysis, whereas $Scto_2$ was not associated. This result suggests that the degree of impairment of autoregulatory function might be a more sensitive marker of brain injury than brain perfusion itself.

While individual improvement in CVAR was observed over 3 days, TOx overall remained different between survivors and non-survivors. The relatively impaired CVAR observed early in survivors was still compatible with good outcomes. The lack of any patients with a poor neurological status precluded any further analysis of the degree of CVAR disturbances across a spectrum of neurological recovery.

A strong positive correlation between TOx and a validated index of autoregulation (Mx), using transcranial Doppler ultrasound, has been reported.[21] The cut-off for TOx to discriminate between survivors and non-survivors based on impaired CVAR in our study was > 0.09 overall and > 0.14 for Day 1, which correlates to Mx of 0.3–0.4. This is very similar to earlier findings in patients with severe sepsis or septic shock, in whom Mx > 0.3–0.4 characterised patients with sepsis-associated delirium.[4,5] While the TOx cut-off to distinguish intact from impaired CVAR is arguably arbitrary, depending on study population characteristics, NIRS equipment and statistical approaches, the outcome-derived criterion obtained by us is still within a range of functional CVAR reported in earlier studies of populations without sepsis.[22,23] Our results emphasise the importance of the degree to which CVAR is impaired in septic shock, even if autoregulatory capacity might not be entirely lost.

The TOx value that identified the most favourable or optimal autoregulatory capacity, opt-TOx, was different in survivors compared with non-survivors on all study days. Interestingly, a further deterioration of opt-TOx was observed in non-survivors, but it remained stable in survivors. We showed a sixfold increase in the OR for survival for an opt-TOx consistent with functional CVAR, based on a dichotomised opt-TOx (≥ 0.09 or < 0.09), which is similar to that used for Mx in an earlier study.[5] Based on data for Day 3, the OR for survival was not significant. Neither was Mx at Day 3 significant for identification of subsequent sepsis-associated delirium.[5] Finally, the recovery of opt-TOx in our study was very similar to that of Mx over the first 4 days of severe sepsis, and highlights the dynamic nature of sepsis-induced disturbances to CVAR. The MAP associated

with opt-TOx was within the clinically accepted target of > 65 mmHg.[14] Whether targeting a higher MAP during septic shock could have improved opt-TOx could not be determined with our purely observational data. A previous multicentre study comparing a target MAP of 65–70 mmHg with 80–85 mmHg in patients treated for septic shock did not show any difference in mortality at 3 months.[24] An association between blood pressure excursions below the lower limit for CVAR and renal impairment[23] and major comorbidity[25] has previously been reported in patients without sepsis. The issue of whether opt-TOx-targeted blood pressure management in septic shock can improve extracerebral organ function warrants further investigation.

Strengths and limitations

We did not explore mechanisms to explain impaired CVAR. A potential for extracerebral perfusion to confound absolute NIRS values has been reported,[26] in particular when comparing NIRS-derived cerebral blood flow measurements with other techniques to measure acute changes in blood flow.[27] The TOx analyses that we report used relative correlating changes in Sct_{O_2} and arterial pressure during stable conditions over more than an hour, which is similar to previous validation studies.[10-12,28] Slow-wave oscillations were present, allowing for opt-TOx to be calculated in most patients (23 out of 28), which was a higher proportion than previously reported in patients with traumatic brain injury.[29]

Our study was limited by the small sample size and the limited duration of recordings, and represents an exploratory feasibility study. The post-hoc computed achieved power for the observed difference in TOx between survivors and non-survivors for Days 1–3 was nevertheless 89%. Our study strengths include that we made consecutive measurements over 3 days, with sufficient time for data sampling (> 30 minutes[12]); we had standardised MAP and $Paco_2$ goals; and we had complete follow-up at 3 months. Further work is needed to validate TOx in a larger patient population, and ultimately a study evaluating haemodynamic support tailored to optimise CVAR against patient-centred outcomes should be considered.

Conclusion

CVAR, as assessed by TOx, was impaired in patients admitted to the ICU for septic shock and was independently associated with mortality. Monitoring TOx is feasible at the ICU bedside and might potentially prove useful to guide haemodynamic management and to improve outcomes in patients with septic shock.

Competing interests

None declared.

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