Original Article

ISSN: 1735-0344 *Tanaffos 2025; 24(2): 187-193*

TANAFFOS

Observational Examination of Cerebral Perfusion Changes in Patients Diagnosed with Sepsis Using Transcranial Doppler Ultrasonography

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Received: 20 January 2025
Accepted: 10 May 2025

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Background: Sepsis-associated Brain Dysfunction (SABD) affects over 70% of septic patients, often manifesting early and increasing the risk of neurological sequelae if undiagnosed. Transcranial Doppler (TCD) ultrasonography is a non-invasive, bedside method to assess Cerebral Blood Flow (CBF). This study evaluates temporal changes in middle cerebral artery blood flow in septic patients using Pulsatility Index (PI), Resistance Index (RI), and CBFi at 0, 6, 24, and 48 hours.

Materials and Methods: Forty-seven septic patients admitted to the Bursa Uludag University Intensive Care Unit were prospectively studied. Demographic data, comorbidities, Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II scores, vital signs, laboratory parameters, and TCD measurements (PI, RI, CBFi) were recorded at baseline, 6, 24, and 48 hours.

Results: No statistically significant changes were observed in PI, RI, or CBFi at 6, 24, or 48 hours compared to baseline ($p>0.05$), though slight increases in PI (2.13%) and CBFi (16.99%) were noted at 48 hours. A significant difference in PI was found at 48 hours in patients receiving vasoactive drugs ($p<0.05$), and in RI at 6 hours in those receiving sedoanalgesics ($p<0.05$). Stable systemic hemodynamics were maintained using advanced monitoring.

Conclusion: In septic patients with optimized hemodynamic management, cerebrovascular resistance and perfusion indices (PI, RI, CBFi) remain largely stable within 48 hours, suggesting effective autoregulation. TCD shows potential as a tool to monitor cerebral perfusion and guide therapy in sepsis, warranting further research.

Keywords: Sepsis; Transcranial Doppler; Cerebrovascular circulation; Ultrasonography; Middle cerebral artery velocity

INTRODUCTION

Sepsis-associated brain dysfunction (SABD), the most common organ dysfunction associated with sepsis, affects approximately 70% of septic patients and frequently manifests in the early stages, often preceding the involvement of other organs (1). Delayed diagnosis of SABD increases the likelihood of neurological sequelae and poses diagnostic challenges (2). In addition to changes resulting from the direct effects of inflammatory mediator release on the brain due to sepsis, systemic effects such as hypotension, stroke, seizures, hypoglycemia, hepatic and renal impairments can secondarily exacerbate cerebral damage (3).

Transcranial Doppler Ultrasonography (TCD) is a non-invasive, repeatable method that can be applied at the bedside in the intensive care unit (ICU) to rapidly assess Cerebral Blood Flow (CBF) associated with sepsis (4-5). TCD is used to evaluate blood flow in the Willis polygon and the vertebrobasilar artery system.

This study aims to investigate the recognition of early cerebral dysfunction in septic patients admitted to the ICU by examining changes in CBF, influencing factors, and alterations in flow resistance indices including Pulsatility Index (PI), Resistivity Index (RI), and CBF Index (CBF_i).

MATERIALS AND METHODS

Following approval from the Bursa Uludağ University Faculty of Medicine Ethics Committee on February 19, 2020, with decision number 2020-3/35, our study was prospectively planned to be conducted in the 21-bed general ICU of Bursa Uludağ University Faculty of Medicine between March 2020 and September 2020, involving patients admitted with a diagnosis of sepsis.

The study included patients aged 18 years and older who were admitted to the ICU with a diagnosis of sepsis within 24 hours of receiving the diagnosis. Sepsis was defined according to the standard international Sepsis-3 criteria (6).

Patients meeting one or more of the following criteria were excluded from the study:

1. Known cerebrovascular lesions (ischemic or hemorrhagic cerebrovascular events, neoplasms)
2. Central nervous system infections (meningitis, encephalitis)
3. Encephalopathy (associated with liver failure, hyperuremia, hyponatremia, or hypoglycemia)
4. Drug intoxication
5. Severe carotid stenosis (>70%)
6. Dementia
7. Pregnancy
8. History of intracranial surgery
9. Individuals under 18 years of age

Patients' demographic information (age, gender), comorbidities, and primary diagnoses were recorded. The Sequential Organ Failure Assessment (SOFA) score was calculated at 0, 6, 24, and 48 hours, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated at 24 hours.

Following admission to the ICU, vital signs (heart rate, Mean Arterial Blood Pressure (MAP), oxygen and mechanical ventilation support status, Positive End-Expiratory Pressure (PEEP)), ICU length of stay, administration of vasoactive, sedative and analgesic medications, renal replacement therapy, total fluid infusion volume, C-reactive Protein (CRP), glucose, arterial blood gas parameters (pH, Partial Pressure of Oxygen (PaO_2), Partial Pressure of Carbon Dioxide ($PaCO_2$), lactate), Oxygen Saturation (SpO_2), PaO_2/Fraction of Inspired Oxygen (P/F) ratio and Glasgow Coma Scale (GCS) scores were recorded at baseline, 6, 24, and 48 hours.

Under standard conditions in our ICU, patients' biochemical laboratory tests, including urea, sodium (Na), and hemogram parameters (Hemoglobin and Hematocrit), are routinely measured at 24-hour intervals. Consequently, the values of Na, urea, HB, and HCT were recorded at baseline and at 24 and 48 hours.

The Mean Velocity in the Middle Cerebral Artery (VMCA), Peak Systolic Velocity (PS), and End-Diastolic Velocity (EDV) were measured at baseline, 6, 24, and 48 hours after the patient's admission to the ICU. Measurements were obtained using the TCD mode of a 2-MHz Doppler probe through the temporal bone window on both sides of the skull. The side with the highest VMCA during the initial measurement was used for subsequent measurements. All patients in the study were assessed with the LogiQ-E7 General Electric ultrasound device.

Each measurement was repeated three times, and the highest value was recorded. All measurements were performed by the same individual using the same device with consistent settings for TCD.

Using the measured values, PI=[Systolic Velocity − Diastolic Velocity] / Mean Velocity, RI=[Systolic Velocity −

Diastolic Velocity] / Systolic Velocity, and Cerebral CBF_i were calculated (4,7)

The baseline parameters and values measured using the TCD method were recorded as initial basal values and statistically compared with the parameters and values measured at 6, 24, and 48 hours.

Statistical Analysis

In our study, the normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while discrete variables were reported as median (interquartile range). Categorical variables were presented with their respective counts and percentages. The significance of differences in PI, RI, and CBF_i between 0–6 hours, 0–24 hours, and 0–48 hours was evaluated using the Wilcoxon Signed-Rank Test. For intergroup comparisons of these measurements, percentage changes in values obtained at different time points relative to baseline (0 hours) were calculated, and these percentage changes were compared between groups using the independent two-sample t-test or the Mann-Whitney U test. Correlation analysis was performed to examine relationships between continuous variables, utilizing the Spearman correlation coefficient. Data analysis was conducted using SPSS (IBM Corp., 2013). IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. A Type I error level of 5% was set for statistical comparisons.

RESULTS

Of the 60 patients admitted to the ICU with a diagnosis of sepsis, 47 were included in the study. During data analysis, 13 patients were excluded for the following reasons: Three patients died within 48 hours of admission, four patients were transferred to other clinics, two patients had a history of cerebrovascular events, and four patients could not be assessed using TCD. The demographic characteristics, comorbidities, sepsis sources, and mechanical ventilation status of the patients were presented (Table 1). The 14-day mortality rate in the ICU for all patients was calculated as 25.53% (n=12), and the 28-day mortality rate was 34.04% (n=16).

Table 1. Demographics, comorbidities, source of infection, and mechanical ventilation distribution of the patients

Age (year) (Mean±SD)	62.3±17
Gender (Female/Male) (n)	21/26
Comorbidities (%)	
Cardiac (HT, CAD, HF)	51.1
DM	38.3
Pulmonary (Asthma, COPD)	19.1
Liver failure	16.7
Malignancy	19.1
Post CPR	14.9
Renal Failure (Acute, Chronic)	51.1
Sepsis Source (n)	
Pneumosepsis	41
Urosepsis	3
Abdominosepsis	3
Septic Shock (n)	26
APACHE II score (Mean±SD)	17.3±6,8
GCS (Mean±SD)	8.8±4.0
MAP (mmHg) (Mean±SD)	79.4±14,4
SOFA (initial) score (Mean±SD)	9±4.0
SOFA (final) score (Mean±SD)	8±3.1
Fluid Infusion (ml/48hour) (Mean±SD)	5127±2146
ICU length of stay (day) (Mean±SD)	19.6±22,2
Hemodialysis (n)	13
Mechanical Ventilation (n)	
NIV	4
IMV	37

MAP: Mean arterial blood pressure, APACHE: Acute physiology and chronic disease evaluation score, GCS: Glasgow coma scale, SOFA: Sequential organ failure assessment, CRP: C-reactive protein, ICU: Intensive care unit, HT: Hypertension, CAD: Coronary artery disease, HF: Heart failure, DM: Diabetes mellitus, COPD: Chronic obstructive lung disease, HBV: Hepatitis B virus, HCV: Hepatitis C virus, CPR: Cardiopulmonary resuscitation, NIV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

No statistically significant differences were found between the percentage changes in glucose, Na, urea, Hb, and Hct, pH, PaO_2, $PaCO_2$, lactate, SpO_2, P/F ratio, PEEP, GCS, and SOFA scores at 6, 24, and 48 hours relative to baseline and the percentage changes in PI, RI and CBF_i at 6, 24, and 48 hours relative to baseline ($p>0.05$).

In the analysis of temporal changes in TCD parameters, no statistically significant differences were observed in the percentage changes of the PI, RI, and CBF_i at 6, 24, and 48 hours compared to baseline ($p>0.05$) (Table 2). Although

slight median increases were noted in PI and CBF_i at 48 hours (2.13% and 16.99%, respectively), these changes did not reach statistical significance. Specifically, PI increased from 1.48±1.06 at baseline to 1.55±1.03 at 6 hours and then decreased to 1.35±1.13 by 48 hours, while RI remained relatively stable, ranging from 0.66 ± 0.21 at baseline to 0.63±0.17 at 48 hours, and CBFi increased from 553.25±338.61 at baseline to 605.70±338.94 at 48 hours. These findings suggest that, within the first 48 hours of sepsis management, cerebrovascular flow and resistance parameters remained largely stable.

Table 2. Temporal changes in transcranial Doppler measured parameters

	(n=47)	IQR	p value
P.I			
%Δ0 Hours →6 Hours	MED %0.00	IQR 56.46	0.709
%Δ0 Hours →24 Hours	MED %0.00	IQR 69.50	0.737
%Δ0 Hours →48 Hours	MED %↑2.13	IQR 107.77	0.434
R.I			
%Δ0 Hours →6 Hours	MED %↓1.59	IQR 30.58	0.628
%Δ0 Hours →24 Hours	MED %0.00	IQR 36.24	0.909
%Δ0 Hours →48 Hours	MED %↑1.69	IQR 46.36	0.526
CBF_i			
%Δ0 Hours →6 Hours	MED %↑1.33	IQR 82.53	0.654
%Δ0 Hours →24 Hours	MED %0.00	IQR 87.08	0.717
%Δ0 Hours →48 Hours	MED %↑16.99	IQR 97.66	0.458

P.I: Pulsatility index, R.I: Resistance index, CBFi: Cerebral blood flow index, MED: median, IQR: Interquartile Range

When patients were divided into groups receiving and not receiving vasoactive drugs, no statistically significant differences were observed in the PI, RI, and CBF_i measurements or in their percentage changes at 6, 24, and 48 hours relative to baseline between the two groups ($p > 0.05$) (Figure 1). When the two groups were combined, and the RI and CBF_i values of all patients were analyzed, no statistically significant differences were found in the percentage changes at 6, 24, and 48 hours relative to baseline ($p>0.05$). However, a statistically significant difference was observed in the PI values at 48 hours relative to baseline ($p<0.05$).

Sedative analgesic treatment was administered to 50% of the patients included in the study, with midazolam used in 5 patients and opioids in 19 patients. When patients were divided into groups receiving and not receiving sedoanalgesic drugs, no statistically significant differences were observed in PI, RI, and CBF_i measurements or in their percentage changes at 24 and 48 hours relative to baseline between the two groups ($p > 0.05$). However, a statistically significant difference was found in the RI values at 6 hours relative to baseline in the group receiving sedoanalgesic drugs ($p<0.05$) (Figure 2). When the two groups were combined, and the PI, RI, and CBF_i values were analyzed, no statistically significant differences were found in the percentage changes at 6, 24, and 48 hours relative to baseline ($p>0.05$).

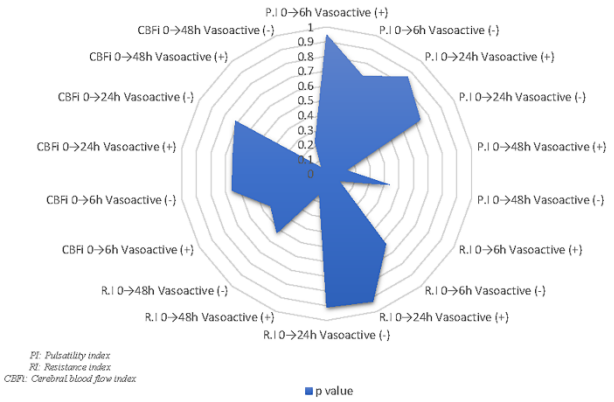

Figure 1. The Effect of Vasoactive Drug Administration on Pulsatility Index, Resistance Index, and Cerebral Blood Flow Index Measurements

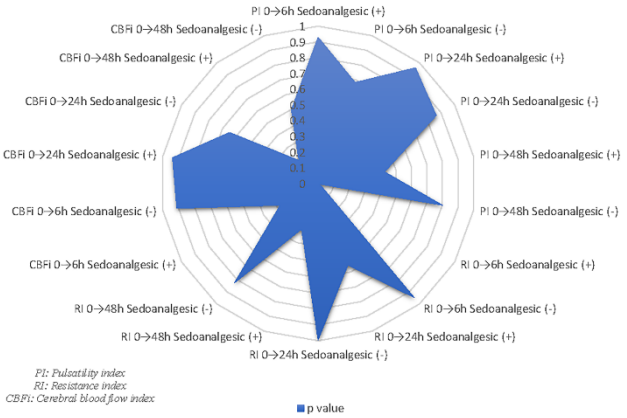

Figure 2. The Effect of Sedoanalgesic Drug Administration on Pulsatility Index, Resistance Index, and Cerebral Blood Flow Index Measurements

DISCUSSION

The relationship between sepsis and cerebral perfusion is intricate and not yet comprehensively understood. Despite frequent alterations in peripheral vascular tone and systemic hemodynamics during sepsis, cerebrovascular autoregulation may remain preserved or exhibit only minimal impairment in the early stages of sepsis. In our study, no statistically significant variations were observed in PI, RI, or CBF_i values over the 48 hours, even in patients requiring vasoactive agents to sustain arterial blood pressure.

The results of our study diverge from the dynamic cerebral hemodynamic patterns documented in the systematic review by de Azevedo et al. (8). That review delineated a characteristic temporal progression during sepsis, characterized by early cerebral vasoconstriction, evidenced by elevated PI and mean flow velocity, followed by late vasodilatation and compromised cerebral autoregulation. We believe that the absence of such a response in our study may be attributed to the implementation of an individualized hemodynamic management protocol in our ICU. In contrast to many studies reported in the literature, our approach incorporated advanced hemodynamic monitoring technologies, including PiCCO (Getinge AB, Göteborg, Sweden), ProAQT (Getinge AB, Göteborg, Sweden), and bedside echocardiography to precisely tailor fluid resuscitation to each patient's volume status. Consequently, patients were maintained in a balanced state, avoiding both volume depletion and fluid overload, conditions known to precipitate fluctuations in cerebrovascular tone and autoregulation. Thus, the lack of discernible trends in vasoconstriction or vasodilatation within our cohort likely reflects the maintenance of stable cerebral perfusion facilitated by optimized fluid and vasopressor therapy.

Moreover, we avoided excessive tidal volumes and refrained from using excessive PEEP levels, which are known to increase intrathoracic pressure and reduce venous return, thereby potentially decreasing cardiac output and cerebral perfusion. A previous study by Videtta et al. (9) demonstrated that high PEEP levels (15 cm H_2O) can elevate ICP in patients with brain injury, but not in patients without intracranial pathology. In our cohort, PEEP levels were maintained within a moderate range, and none of the patients required plateau pressures above accepted thresholds. This likely contributed to the stable PI and RI values, as elevated PEEP can indirectly impair cerebral perfusion.

Importantly, our study proactively mitigated hypotension, a primary contributor to impaired cerebral perfusion. MAP was consistently maintained above 65 mmHg in all patients through early and individualized vasopressor support. This strategy aligns with the current understanding that hypotension is a critical determinant of cerebral hypoperfusion and compromised autoregulation in patients with sepsis. Prior research has demonstrated that reduced MAP impairs cerebral microcirculation, potentially precipitating neurological dysfunction and adverse clinical outcomes (10–12).

In contrast to previous research associating vasoactive agent use with alterations in cerebral hemodynamics (13), our study identified only a modest elevation in PI at 48 hours among patients receiving vasopressors, with no corresponding changes in RI or CBF_i. This observation may suggest a transient, potentially subclinical increase in cerebrovascular resistance or could reflect the inherent variability of PI under stable systemic hemodynamic conditions.

Furthermore, while prior studies have indicated that opioids and sedatives may influence cerebral perfusion by modulating ICP or CBF (14-17), our investigation found no sustained differences in CBF parameters among patients receiving sedation and analgesia. A statistically significant increase in RI was observed at 6 hours in the sedated cohort; however, this effect was transient, resolving by 24 and 48 hours, and was not accompanied by alterations in PI or CBF_i.

This study is subject to several limitations. First, while advanced hemodynamic monitoring technologies were

employed following admission to the ICU, comprehensive data regarding the type and volume of fluids administered in the emergency department or ward before ICU admission were unavailable. This lack of pre-ICU data may have confounded the assessment of early cerebral hemodynamics. Second, TCD measurements are inherently operator-dependent and susceptible to variations arising from factors such as insonation angle and temporal window quality. Despite efforts to standardize procedures and the use of a single experienced operator, some degree of measurement variability cannot be entirely excluded.

Third, the study's sample size was relatively small, potentially limiting the statistical power to detect subtle alterations in cerebral perfusion parameters or to conduct robust subgroup analyses, such as comparisons between patients with septic shock and those without. Fourth, although patients with known cerebrovascular pathology were excluded, routine neuroimaging was not performed, raising the possibility that occult structural lesions may have gone undetected. Fifth, TCD does not directly measure intracranial pressure or cerebral perfusion pressure, and surrogate indices, such as PI and RI, may be influenced by systemic factors unrelated to cerebral perfusion.

Finally, the absence of long-term neurological outcome data restricted our ability to correlate early TCD findings with clinical endpoints, such as delirium, cognitive impairment, or mortality, thereby limiting the broader implications of our results.

CONCLUSION

Our results indicate that in septic patients, cerebral blood flow and vascular resistance remain predominantly stable during the initial 48-hour period, provided systemic hemodynamics are optimized through advanced monitoring techniques. The absence of statistically significant alterations in TCD indices likely reflects the efficacy of individualized fluid resuscitation, vasopressor administration tailored to volume status, avoidance of excessive PEEP, and maintenance of normotension.

In contrast to previous studies reporting early cerebral vasoconstriction or late vasodilatation in sepsis, our proactive and protective hemodynamic management strategy may have mitigated such cerebrovascular extremes. These findings highlight the potential utility of TCD as a non-invasive tool for monitoring and validating resuscitation strategies in the ICU.

Acknowledgements

We express our sincere gratitude to the medical and nursing staff of the Bursa Uludağ University Faculty of Medicine ICU for their invaluable support in patient care and data collection. We also thank the Bursa Uludağ University Faculty of Medicine Ethics Committee for their guidance and approval of this study. No external financial support was received for this study.

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