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REVIEW PAPER

Cerebral hemodynamics in sepsis assessed by transcranial Doppler: a systematic review and meta-analysis

Daniel Silva de Azevedo[1] · Angela Salomao Macedo Salinet[1] · Marcelo de Lima Oliveira[1] · Manoel Jacobsen Teixeira[1] · Edson Bor-Seng-Shu[1] · Ricardo de Carvalho Nogueira[1]

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Abstract Cerebral microcirculation is gradually compromised during sepsis, with significant reductions in the function of capillaries and blood perfusion in small vessels. Transcranial Doppler ultrasound (TCD) has been used to assess cerebral circulation in a typical clinical setting. This study was to systematically review TCD studies, assess their methodological quality, and identify trends that can be associated with the temporal evolution of sepsis and its clinical outcome. A meta-analysis of systematic reviews was conducted according to the PRISMA statement. Articles were searched from 1982 until the conclusion of this review in December 2015. Twelve prospective and observational studies were selected. Evaluations of cerebral blood flow, cerebral autoregulation, and carbon dioxide (CO_2) vasoreactivity were summarized. A temporal pattern of the evolution of the illness was found. In early sepsis, the median blood flow velocity (Vm) and pulsatility index (PI) increased, and the cerebral autoregulation (CA) remained unchanged. In contrast, Vm normalization, PI reduction and CA impairment were found in later sepsis (patients with severe sepsis or septic shock). Cerebral haemodynamic is impaired in sepsis. Modifications in cerebral blood flow may be consequence to the endothelial dysfunction of the microvasculature induced by the release of inflammatory mediators. A better understanding of cerebral hemodynamics may improve the clinical management of patients with sepsis and, consequently, improve clinical outcomes.

✉ Edson Bor-Seng-Shu
edsonshu@gmail.com

[1] Neurology Department, School of Medicine, Hospital das Clinicas, University of São Paulo, Avenida Doutor Arnaldo, 455, Cerqueira César, São Paulo, SP CEP 01246-904, Brazil

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1 Introduction

Hemodynamic impairment is a key feature of sepsis. Cerebral microcirculation may be gradually compromised, with significant changes in cerebral blood flow (CBF), which may play a role in the etiology of encephalopathy associated with sepsis (EAS) [1]. EAS is a brain dysfunction that develops in more than 50 % of intensive care unit (ICU) patients, and it is one of the most common causes of delirium in ICUs. Moreover, EAS can be associated with increased mortality [2–5].

There are several methods applied to evaluate CBF during sepsis. However, to date, there has been no information indicating the best method [6–8]. Transcranial Doppler ultrasound (TCD) is an attractive option due to its portability and real-time detection of changes in cerebrovascular hemodynamics at bedside [9, 10]. The measurement of CBF velocity (CBFV) with TCD can be considered a surrogate of CBF, if it is assumed that the diameter of the vessel remains constant. Therefore, the changes in CBFV detected by TCD could represent the hemodynamic changes mediated by microcirculation [11]. In addition, the simultaneous measurement of CBFV with other variables, such as arterial blood pressure and end tidal CO_2, may provide significant information about the mechanisms involved in the regulation of CBF [12–14]. Thus, TCD monitoring of patients with sepsis will likely provide valuable information about cerebral hemodynamic changes and correlate with the prognostic determinants of the disease. In addition, the study of cerebral

hemodynamics in the acute phase of sepsis may elucidate some physiopathological aspects of the syndrome. However, the literature lacks information on the relationship between TCD parameters and the longitudinal modulation of cerebral hemodynamics after sepsis [9, 11].

The objectives of this review are to (1) systematically evaluate TCD studies in patients with sepsis; (2) identify the cerebral hemodynamic course of the disease; and (3) perform a meta-analysis of the cerebral hemodynamic parameters.

2 Methods

We searched for studies that evaluated cerebral hemodynamic changes in patients with sepsis in the PUBMED, MEDLINE and EMBASE databases. Articles with publication dates ranging from January 1982 to December 2015 were included in the search. The terms used for the search were: "brain perfusion in sepsis", "sepsis and transcranial Doppler", or "EAS and transcranial Doppler". The bibliographical references of the retrieved articles were also analyzed and included if relevant. The inclusion criteria were as follows: (1) prospective studies in which TCD was the method applied for evaluation of cerebral hemodynamics; (2) studies that included patients with sepsis or septic shock according to international standardized diagnostic criteria; and (3) studies that were approved by an institutional ethics committee. The exclusion criteria were as follows: (1) studies that included patients under 18 years of age; (2) studies that included patients with a previous neurological impairment; (3) experimental human studies; (4) non-human studies; and (5) non-English publications.

Two independent researchers (D.S.A. and A.S.M.S.) evaluated the quality of the selected studies through a 12-item checklist (Tables 1, 2), according to the "PRISMA Statement" [15]. For a descriptive analysis of each study, the following data were extracted: number of patients included, study type, methodology, main findings of the hemodynamic assessment, outcomes, study limitations, conclusions and quality assessment of the article.

The articles were grouped according to parameters derived from TCD studies, as follows: CBF parameters (mean CBFV, mCBFv; systolic CBFV, sCBFv; diastolic CBFV, dCBFv; pulsatility index, PI); static and/or dynamic cerebral autoregulation (sCA and dCA, respectively); and CBF reactivity to carbonic gas ($CRCO_2$).

For the meta-analyses, the variables were compared in septic versus nonseptic phases and/or early versus late stages (24 and 48 h after diagnosis, respectively). The software used was the OpenMetaAnalyst (Center for Evidence-based Medicine, Brown University School of Public Health, Providence, RI, USA). The analysis was performed using the random effects model, the weighted mean difference (MD) was used for the measurement data and the 95 % confidence interval (CI) was used as the effect indicator for the dichotomous variables. The heterogeneity assumption was checked by the χ^2-based Q test.

3 Results

The searches in PUBMED, MEDLINE and EMBASE retrieved 152 articles. After analyzing the title and abstract and discarding duplicates, 46 articles were deemed suitable. The inclusion and exclusion criteria were applied, leaving 16 articles for further analysis (Fig. 1). As presented in Table 2, the median score of the proposed quality checklist was 11 out of 12 (range 9–12). A summary of the main findings of each article is provided in Table 3.

After grouping the articles based on pre-specified TCD derived variables, the common findings were as follows:

3.1 sCA and dCA

sCA or dCA were assessed in four studies, all of which were observational, with a total of 70 patients included. Three studies evaluated sCA [1, 17, 18], and one evaluated dCA [19]. They demonstrated impaired autoregulation in the late sepsis phase [1, 18, 19] and unchanged regulation in the early phase [17]. The median score on the proposed quality checklist of these studies was 11 (range 9–12). The limitations were small numbers of patients evaluated and methodological variability of the CA analyses.

3.2 $CRCO_2$

Seven studies, all of which were observational (one controlled), evaluated the $CRCO_2$, with a total of 110 patients included. Three studies showed a reduction of $CRCO_2$ in septic patients [20–22], three studies described CO_2 reactivity as unchanged [17, 18, 23] and one study demonstrated that CO_2 reactivity was variable [16]. The median score on the proposed quality checklist of these studies was 11 (range 9–12). The limitations were small numbers of patients evaluated, different vasodilatory stimuli (CO_2 or acetazolamide), different cutoff values and methodological variability of the $CRCO_2$ analyses.

3.3 Cerebral blood flow parameters

Seven studies, all of which were prospective observational studies (four controlled), evaluated TCD variables, with a total of 152 patients included. The main finding from the majority of the studies was a decrease of the mCBFv in sepsis [20–22, 24]. However, one study showed an increase

Table 1 PRISMA criteria adapted

Items rated	Criteria	
Summary and methodology		
Objectives and assumptions described in the introduction or methodology	The objectives and hypotheses of researchers are described in the introduction or methodology	A
Description of the study population	The study population is described in detail (e.g., age, comorbidities)	B
Ethical principles with informed consent	Informed consent was obtained from patients/controls in accordance with the approved guidelines of the local ethics committee	C
Criteria for inclusion and exclusion	Inclusion and exclusion criteria are clearly described	D
Relationship between the variables is presented based on statistical validation tests	Relationship between the dependent and independent variables is tested with statistical significance tests	E
EBF, EBFi, PI, ReA, ARD, and RCO_2 are clearly presented and consistent	Calculations of EBF, EBFi, PI, ReA, ARD, and RCO_2 are presented	F
Results		
Specification of the relevant characteristics of the patients	Age and sepsis severity classification are presented	G
Graphs and tables summarize the results	Graphics and tables are presented with a summary of relevant results for completion of the study	H
Reproducible data	The study tested the validity of the measures based on established criteria	I
Discussion		
Considerations of and alternatives to results found	The results of each completed objective are discussed	J
Discussion of limitations	Limitations of the study are presented and discussed	K
Future research	Suggestions for future research are made	L

Table 2 Quality of studies using the criteria proposed in the PRISMA statement

Study	Criteria												Total
	A	B	C	D	E	F	G	H	I	J	K	L	
Pierrakos et al. [10]	1	1	1	1	1	1	1	1	1	1	1	1	12
Pierrakos et al. [9]	1	1	1	1	1	1	1	1	1	1	1	1	12
Fülesdi et al. [24]	1	1	1	1	1	1	1	1	1	1		1	11
Szatmári et al. [20]	1	1	1	1	1	1		1	1	1		1	10
Taccone et al. [1]	1	1	1	1	1	1	1	1	1	1	1	1	12
Steiner et al. [19]	1	1	1	1	1	1	1	1	1	1	1		11
Pfister et al. [18]	1	1	1	1	1	1	1	1	1	1	1	1	12
Kadoi et al. [22]	1	1	1	1	1	1	1	1	1	1	1		11
Thees et al. [23]	1	1	1	1	1	1	1	1	1	1		1	11
Bowie et al. [16]	1	1	1	1	1	1	1	1	1	1	1	1	12
Terborg et al. [21]	1	1	1	1	1	1	1	1	1	1			10
Matta and Stow [17]		1	1	1	1	1	1	1	1	1			9
Total	11	12	12	12	12	12	11	12	12	12	7	8	

in the mCBFv, and one study demonstrated that this parameter was not altered. Three studies evaluated the dCBFv, and two evaluated sCBFv. They concluded that in sepsis, there is an increase in systolic velocity [9, 24] and a decrease in diastolic velocity [9, 20, 24]. All studies demonstrated a PI increase in sepsis [9, 10, 20–24]. The median score on the proposed quality checklist of the studies was 11 (range 10–12). The limitations were different stages of evaluation of the CBF parameters and heterogeneity of the evaluated groups.

3.4 Meta-analysis

For the meta-analysis, only the variables mCBFV, sCBFv, dCBFv and PI remained suitable. The other variables had to be excluded due to different methodology, different stimuli and different cutoff values.

The studies that evaluated CBFV in septic versus non-septic patients showed a non-significant mCBFV decreased in sepsis (mean −1.42; heterogeneity $p = 0.151$ and 95 % CI −5.22 to 2.37—Table 4), and it was associated with a

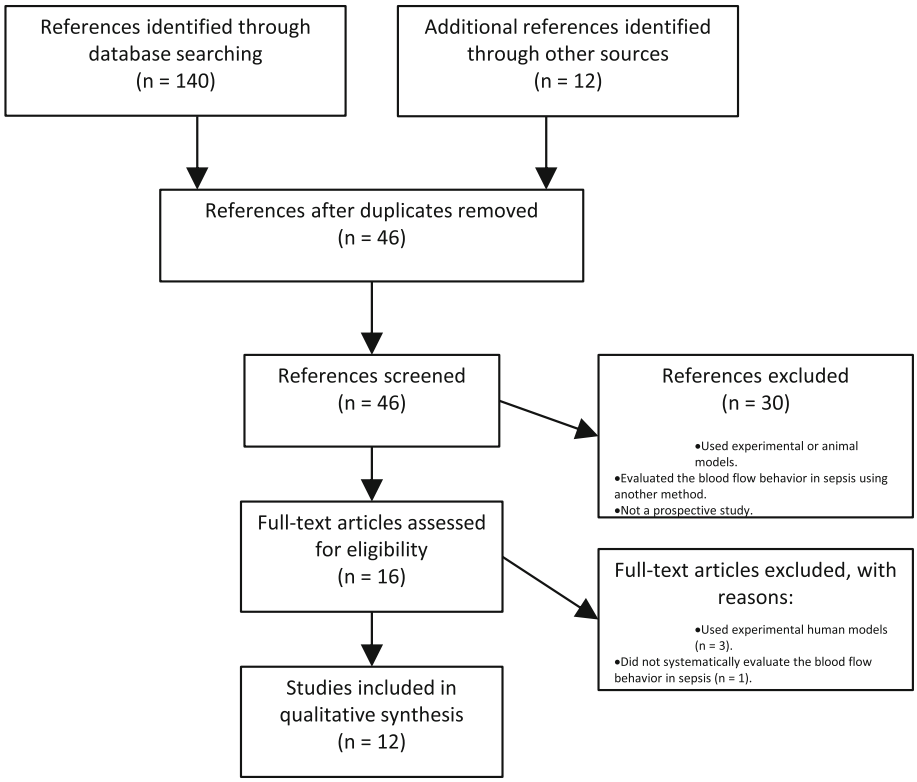

Fig. 1 Flow diagrams of the study selection process

significant increase in PI (mean 0.18; heterogeneity $p < 0.001$ and 95 % CI 0.03–0.33—Table 5). The systolic velocity showed a non-significant increase in sepsis (mean 8.09; heterogeneity $p = 0.177$ and 95 % CI −6.41 to 22.60—Table 6), but a non-significant decrease of the diastolic velocity was found (mean −7.83; heterogeneity $p = 0.092$ and 95 % CI −16.63 to 0.96—Table 6).

Regarding the studies that compared the variables at early and late stages, the main findings were a non-significant increase in mCBFV, PI and sCBFV 24 h after the diagnosis of sepsis (mean 22.50; heterogeneity $p < 0.001$ and 95 % CI −11.74 to 56.74; mean 0.01; heterogeneity $p = 0.53$ and 95 % CI −0.17 to 0.03; mean 2.97; heterogeneity $p = 0.22$ and 95 % CI −8.06 to 14.00, respectively—Figs. 2, 3, 4). Conversely, dCBFV showed a non-significant decrease in the first 24 h (mean −0.37; heterogeneity $p = 0.20$ and 95 % CI −5.05 to 4.29—Fig. 5).

4 Discussion

The most important contribution of this review is the identification of cerebral hemodynamic changes in patients with sepsis compared to control subjects, and during the different stages of the disease. The majority of the parameters evaluated in the meta-analysis did not reach significance, due to mostly the heterogeneity of the studies. However, a pattern of hemodynamic behaviour can be speculated. Regarding sepsis stages, a progressive Vm and PI increase (CA remains unchanged) in early phase of sepsis (24 h after the beginning of the sepsis symptoms) were found in the majority of the studies. In contrast, it was described a Vm and PI reduction, and CA impairment in the later phase of sepsis (patients with severe sepsis or septic shock). A description of this phenomenon has not been reported in the literature. The comparison between septic patients and control group revealed Vs increase, Vd decrease, and a consequent PI elevation. These results are in line with those reported in the literature regarding the systemic hemodynamic modifications (blood flow and vascular resistance). The quantitative overview provided by this study supplies evidence that the cerebral hemodynamic parameters behave differently during the phases of the illness.

The significant PI elevation may represent a higher cerebrovascular resistance in sepsis, which has been correlated with a higher prevalence of delirium [9] and coma. The PI is the difference between systolic and diastolic flow velocities divided by the mean velocity, and can represent the tonus of distal cerebrovascular vasculature, it may be influenced by high intracranial pressure, low diastolic blood pressure linked with systemic chock, PCO_2 changes, and systemic blood pressure close to critical closing pressure. Therefore, the PI increase in our revision may be viewed with caution. A recent study [25] showed that PI

Table 3 Characteristics of published studies evaluating CBF by TCD in patients with sepsis

Study	Design	Patients	Mean age	Classification	Evaluation time (h)	Duration	CBF	PI	CBFi
Pierrakos et al. [10]	Prospective, observational	38	67	Sepsis and septic shock	<24 and >72	10 s	Decreased at <24 h and increased or normalized at >72 h	Increased at <24 h and decreased or normalized at >72 h	Decreased at <24 h and increased or normalized at >72 h
Pierrakos et al. [9]	Prospective, observational, controlled	36	67	Sepsis	<48 and >72	–	There was no difference between groups	Increased in the sepsis group ($p = 0.01$)	There was no difference between groups
Fülesdi et al. [24]	Prospective, observational, controlled	16	70	Sepsis and severe sepsis	<24	20 min	There was no difference between groups	Increased in the sepsis group ($p = 0.01$)	–
Szatmári et al. [20]	Prospective, observational, controlled	34	–	Sepsis	–	20 min	Lower diastolic velocities in the sepsis group	Increased in the sepsis group	–
Taccone et al. [1]	Prospective, observational	21	65	Septic shock	<72	20 min	–	–	–
Steiner et al. [19]	Prospective, observational	23	68	Severe sepsis and septic shock	–	60 min	–	–	–
Pfister et al. [18]	Prospective, observational	16	75	Sepsis, severe sepsis and septic shock	>48	–	–	–	–
Kadoi et al. [22]	Prospective, observational	20	65	Severe sepsis	<72	5–10 min	Decrease	–	–
Thees et al. [23]	Prospective, observational	10	50	Severe sepsis	>48	40 min	Normal	–	–
Bowie et al. [16]	Prospective, observational	12	68	Severe sepsis and septic shock	>24	–	–	–	–
Terborg et al. [21]	Prospective, observational	8	60	Severe sepsis	–	–	Increased	–	–
Matta and Stow [17]	Prospective, observational	10	60	Sepsis, severe sepsis and septic shock	<24	–	–	–	–

Table 3 continued

Study	ARe	ARd	RO_2	RCO_2	RVaso	Sedative	Outcome
Pierrakos et al. [10]	–	–	–	–	–	–	Greater delirium in patients with increased PI at <24 h ($p = 0.03$)
Pierrakos et al. [9]	–	–	–	–	–	Propofol or midazolam ($p = 0.63$)	–
Fülesdi et al. [24]	–	–	–	–	–	–	–
Szatmári et al. [20]	–	–	–	Impaired/decreased in the sepsis group	–	–	–
Taccone et al. [1]	Impaired	–	–	–	–	–	–
Steiner et al. [19]	–	Impaired	–	–	–	–	–
Pfister et al. [18]	Impaired	–	–	Normal	–	–	Increased delirium in patients with impaired autoregulation
Kadoi et al. [22]	–	–	–	Decreased (lowest in the group using dexmedetomidine)	–	Dexmedetomidine or propofol	–
Thees et al. [23]	–	–	Normal	Normal	–	Propofol and sufentanil	–
Bowie et al. [16]	–	–	–	Variable	–	–	There was no significant difference
Terborg et al. [21]	–	–	–	Impaired	–	–	–
Matta and Stow [17]	Normal	–	–	Normal	–	–	–

Table 4 Mean values of cerebral blood flow velocity (CBFV) in controls and septic patients included in the meta-analysis

Study	CBFV (cm s^{-1})				
	Controls		Patients		Mean (95 % CI)
	n	Mean (SD)	n	Mean (SD)	
Pierrakos et al. [9]	36	99 (28.0)	36	110 (34.0)	11 (−3.3 to 25.3)
Fülesdi et al. [24]	16	56.6 (10.7)	16	52.9 (29.4)	−3.7 (−19 to 1.6)
Szatmari et al. [20]	20	58.2 (12.0)	14	47.9 (14.5)	−10.3 (−19.5 to −1.0)
Kadoi et al. [22]	20	37.6 (4.75)	20	36.8 (4.1)	−0.7 (−3.5 to 2.0)
Terborg et al. [21]	8	37.6 (4.75)	8	36.8 (4.16)	−0.7 (−5.1 to 3.6)
Total	100		94		−1.4 (−5.2 to 2.3)*

* Heterogeneity, $p = 0.15$

Table 5 Mean values of pulsatility index (PI) in controls and septic patients included in the meta-analysis

Study	PI				
	Controls		Patients		Mean (95 %CI)
	n	Mean (SD)	n	Mean (SD)	
Pierrakos et al. [9]	36	0.98 (0.16)	36	1.15 (0.25)	0.17 (−0.07 to 0.26)
Fülesdi et al. [24]	16	0.84 (0.21)	16	1.16 (0.24)	0.32 (0.16 to 0.47)
Szatmari et al. [20]	20	0.85 (0.20)	14	1.15 (0.35)	0.30 (0.09 to 0.50)
Kadoi et al. [22]	20	1.05 (0.13)	20	1.06 (0.14)	−0.07 (−0.07 to 0.09)
Total	92		86		0.18 (0.03 to 0.33)*

* Heterogeneity, $p < 0.001$

Table 6 Mean values of systolic and diastolic cerebral blood flow velocity (CBFV) in controls and septic patients included in the meta-analysis

Study	sCBFV (cm s^{-1})					dCBFV (cm s^{-1})				
	Controls		Patients		Mean (95 % CI)	Controls		Patients		Mean (95 % CI)
	n	Mean (SD)	n	Mean (SD)		n	Mean (SD)	n	Mean (SD)	
Pierrakos et al. [9]	36	166 (51.0)	36	192 (59.0)	26.0 (0.5 to 51.4)	36	67 (18.0)	36	68 (26.0)	1.0 (−9.3 to 11.3)
Fülesdi et al. [24]	16	85.4 (13.7)	16	94 (42.2)	8.6 (−13.1 to 30.3)	16	45.2 (8.2)	16	34.8 (23.4)	−10.4 (−22.5 to 1.7)
Szatmari et al. [20]	20	85.9 (13.7)	14	85.4 (20.7)	−0.5 (−12.8 to 11.8)	20	45.6 (8.8)	14	32.5 (12.3)	−13.1 (−20.6 to 5.5)
Total	72		66		8.0 (−6.4 to 22.6)*	72		66		−7.8 (−16.6 to 0.9)**

* Heterogeneity, $p = 0.17$

** Heterogeneity, $p = 0.09$

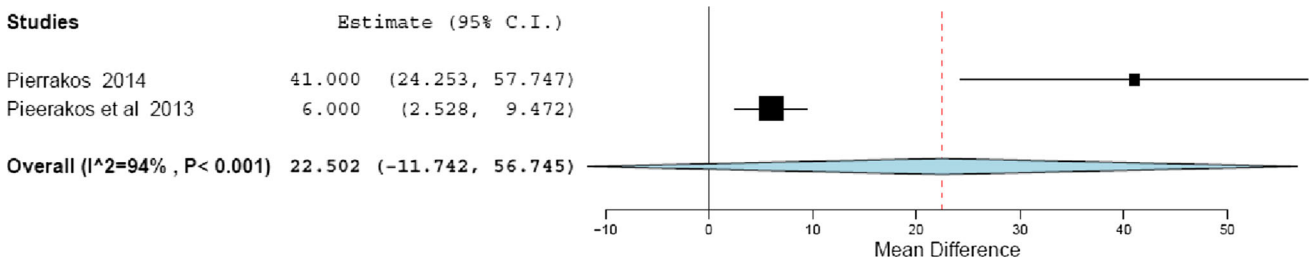

Fig. 2 Statistical analysis of studies that evaluated mean flow velocity in septic patients before and 24 h after diagnosis

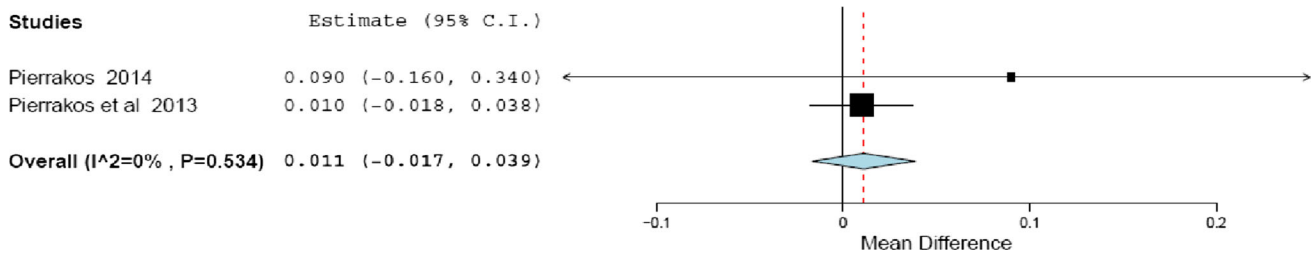

Fig. 3 Statistical analysis of studies that evaluated the PI in septic patients before and 24 h after diagnosis

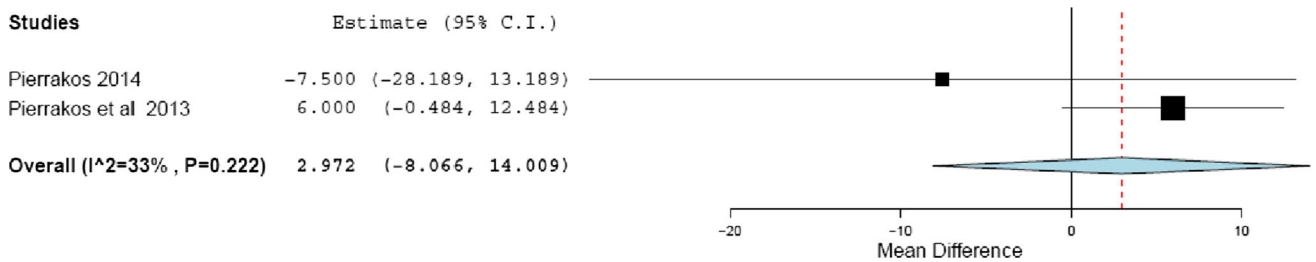

Fig. 4 Statistical analysis of studies that evaluated systolic flow velocity in septic patients before and 24 h after diagnosis

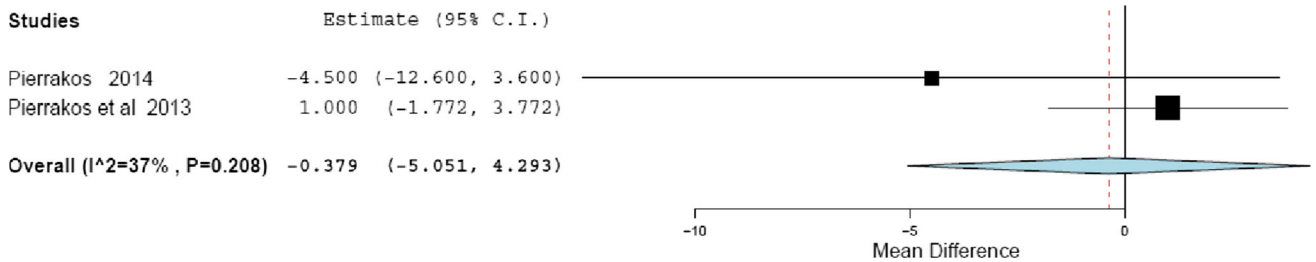

Fig. 5 Statistical analysis of studies that evaluated diastolic flow velocity in septic patients before and 24 h after diagnosis

can not be interpreted alone as an absolute indicator of cerebrovascular resistance, but it can be associated with others parameters [26]. However, in the studies included in this present review, the PCO_2 was controlled (and not varied) and high intracranial pressure was not expected.

When the blood flow behavior was systematically evaluated in septic patients at two different times, a tendency toward an increase in mCBVF, sCBFV, and PI was found 24 h following a diagnosis of sepsis. Although they are not significant, these findings are important because they are correlated with the pathophysiological findings observed in other studies. The endothelial cells of cerebral vessels that are prematurely activated by pro-inflammatory cytokines and endotoxins can reduce the endothelium vasoactive response through nitric oxide (NO), promoting vasoconstriction mediated by prostanoids and endothelins [22, 27, 28]. The activation of nitric oxide synthase (iNOS) by the endothelium is responsible for the overproduction of NO, which may lead to cerebral vascular dilation and counterbalances the early vasoconstrictor response [29]. The subsequent gradual accumulation of NO that occurs throughout all phases of sepsis (primarily during the later phases) may lead to normalization or increase the flow. The increased CBF is also enhanced by mitochondrial dysfunction associated with high lactate production, which is more common at later phases of sepsis [30].

Although the elevated PI indicates an increase in cerebrovascular resistance that may promote a decrease in CBFV, this review demonstrated that the PI increase, evident 24 h after the sepsis diagnosis, was associated with increases in sCBFV and mCBFV. A reasonable explanation for this phenomenon is that vasoconstriction triggers an increase in cardiac output [31] with a disproportional increase in sCBV and a decrease in dCBFV, ultimately leading to a final increase in mCBFV.

Although the quantitative evaluation of cerebral autoregulation was not possible to include in our meta-analysis, 3 of 4 studies demonstrated impairment in autoregulation, which indicated that this phenomenon may occur during sepsis. Most of the studies demonstrated that

sepsis causes a reduction in microvascular reactivity due to NO accumulation, which is also associated with reduced oxygen consumption in tissues [32, 33]. The impairment of CA has been correlated with more severe illness, more frequent occurrence of EAS, high levels of inflammatory biomarkers (C-reactive protein and interleukin-6), neuronal damage (100-beta), and unfavorable prognoses, especially during the later phase [19]. In addition, CA impairment was strongly associated with $PaCO_2$ levels and did not correlate with systemic hemodynamic dysfunction [1, 17, 19]. It is reasonable to conclude, based on these studies, that in addition to a mere evaluation of CBF, the investigation of CA during sepsis may provide a better understanding of the disease and may influence patient management.

There have been conflicting results regarding CO_2 reactivity. In part, this finding may be due to methodological differences during the analysis. In some studies, patients were sedated and on mechanical ventilators, whereas in other studies, patients had spontaneous ventilation. Furthermore, different vasodilatory stimuli (CO_2 or acetazolamide) and different cutoff values were adopted. For this reason, it was not possible to perform a meta-analysis to assess CO_2 reactivity. The reduction in CO_2 reactivity in septic patients may increase the risk of low encephalic perfusion, which can potentially cause encephalic injury, neuronal dysfunction, and a worse neurological prognosis. Pfister et al. [18] showed evidence that independently of the changes in the mean blood pressure (MAP), cerebrovascular CO_2 reactivity was severely compromised. This finding was corroborated by Terborg et al. [21], who demonstrated lower vascular reactivity to CO_2 in septic patients receiving different sedatives.

The majority of studies in this review used APACHE II gravity score or SAPS II score to rank septic patients. No significant association between the scores and their results was found. However, Pierrakos et al. [10] showed a significant difference in APACHE II score and in septic shock, when PI was high. In line with that, vasopressors/inotropes was used in septic patients in all included studies in this review, except Szatmári et al. [20]. No significant influence in their result was described.

Alterations in encephalic perfusion during sepsis contribute to the pathophysiology of EAS. Many factors that lead to CBF alterations (such as alterations in cerebrovascular reactivity and impairment of autoregulation) are frequently the result of dysfunction of the cerebral microvasculature of encephalic tissue due to the release of inflammatory mediators [34]. This fact is most evident when comparing the CBF at two different times after the diagnosis of sepsis.

The use of TCD to assess cerebral hemodynamic patterns has some clinical advantages: (1) TCD can be used to identify cerebral hemodynamic patterns in sepsis that may precede systemic hemodynamic signals; (2) increased PI in confused patients can be an early sign of sepsis and help to decrease the time to diagnosis [9]; and (3) the identification of CBF changes in real time with TCD, correlating with systemic hemodynamic changes, can improve the management of blood pressure and blood volume in septic patients.

The limitations of the studies included in this meta-analysis include the small numbers of patients evaluated, methodological variability, heterogeneity of the evaluated groups, and the presence of only a single controlled and unblinded study, all of which leave these studies with low statistical power. Another important limiting factor is that TCD is operator-dependent. Although the statistical power assessment of the studies is low, the overall methodological quality of each study is good, thus reflecting the good quality of key methodological criteria in most of the studies. This is very relevant to the interpretation of the findings.

5 Conclusion

Certain brain hemodynamic patterns emerge during the evolution of sepsis. This trend points to early cerebral vasoconstriction followed by late vasodilatation with increased CBFV.

The selected studies demonstrated that TCD is an important, accessible, and non-invasive method of evaluating cerebral circulation in patients with sepsis. Although the studies included small numbers of patients with large heterogeneity, their results are relevant due to the good quality of the research. However, new studies with larger numbers of patients and appropriate methodologies are still necessary to allow better correlations of the changes observed with the diverse phases of the illness. Such studies would provide a better understanding of microvascular alterations, thus improving the management of septic patients and possibly their clinical outcomes.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest and manuscript has not been submitted to more than one journal for simultaneous consideration. Moreover, I can confirm that the final version of the manuscript have been reviewed and approved by all authors.

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