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● *Original Contribution*

FLUID RESUSCITATION IN SEPTIC PATIENTS IMPROVES SYSTOLIC BUT NOT DIASTOLIC MIDDLE CEREBRAL ARTERY FLOW VELOCITY

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Abstract—To investigate the effects of fluid resuscitation on cerebral hemodynamics in sepsis, the following set of transcranial Doppler (TCD) parameters was used: maximal change in flow velocity (FV) during stroke onset (acc), maximal FV during first (sys1) or second (sys2) phase of systole and mean diastolic FV (dias@560). We aim to evaluate changes in cerebral hemodynamics that result from (i) sepsis and (ii) adequate fluid resuscitation in critically ill septic patients. In the majority of 16 septic patients sys2 was initially absent but reappeared during the period of fluid resuscitation; whereas sys2 absence was never seen in healthy controls. Second, adequate fluid resuscitation resulted in a significant increase of the systolic FV components (acc, sys1, sys2 and systolic blood pressure); whereas the diastolic components (dias@560 and diastolic blood pressure) remained unchanged. Sys2 absence and reappearance in sepsis suggests that TCD could become a non-invasive alternative for hemodynamic monitoring. (E-mail: a.schaafsma@mzh.nl) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Sepsis, Transcranial Doppler, TCD, Shock, Resuscitation, Intra-cranial hemodynamics.**

INTRODUCTION

Severe sepsis and septic shock are serious medical conditions with high morbidity and mortality rates (Fleischmann et al. 2016; Iwashyna et al. 2010). Sepsis can induce organ dysfunction and failure, as a result of tissue hypoperfusion or systemic hypotension (Dellinger et al. 2013; Levy et al. 2003). The brain is often one of the first organs affected by sepsis, preceding dysfunction of other organ systems (Bolton et al. 1993; Bowton et al. 1989; Maekawa et al. 1991; Sonneville et al. 2013). Reduced cerebral perfusion is assumed to be a precipitating factor for cerebral dysfunction in sepsis and may contribute to the development of sepsis-associated encephalopathy (SAE) (Eidelman et al. 1996; Pfister et al. 2008; Taccone et al. 2013). SAE is a brain dysfunction associated with delirium and increased mortality (Eidelman et al. 1996) that is seen in up to 70% of the septic patients (Papadopoulos et al. 2000; Pfister et al. 2008; Pierrakos et al. 2013).

The purpose of fluid resuscitation is to restore tissue perfusion and oxygenation. It is an essential aspect of the protocol-based and targeted treatment strategy that is recommended in sepsis because it has been shown to reduce mortality (Levy et al. 2010). However, fluid administration should be strictly guided to avoid subsequent overzealous fluid therapy (Dellinger et al. 2013; Marik and Bellomo 2016) as this on itself can compromise tissue perfusion and oxygenation, thereby contributing to organ dysfunction and ultimately organ failure (Lansdorp et al. 2012; Marik and Bellomo 2016; Vincent and Weil 2006). Despite the fact that the brain is often involved, limited information is available about the effects of fluid resuscitation on the cerebral hemodynamics in sepsis (de Azevedo et al. 2016).

Transcranial Doppler (TCD) is a technique that can be used to evaluate changes in cerebral perfusion non-invasively in both healthy patients and critically ill septic patients (Pierrakos et al. 2013). For instance, Pierrakos et al. (2014) studied the pulsatility index (PI) and the association with SAE in septic patients. They found an increased PI on the first day of sepsis that was correlated

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with a higher incidence of delirium. They concluded that the increase in PI, as detected by TCD in the early stage of sepsis, indicates a state of cerebral vasoconstriction and that it is correlated with clinical signs of SAE (Pierrakos et al. 2014).

To gain more insight into the cerebral hemodynamics in sepsis, a recent review by de Azevedo et al. (2016) described cerebral hemodynamic changes in septic patients compared with control patients and during various stages of the disease. This meta-analysis could not find significant changes in TCD parameters during the various stages of sepsis, possibly because of the heterogeneity of the studies (de Azevedo et al. 2016). The failure to reach significance may also be related to the fact that most patients were hemodynamically stable at the time of the TCD measurement. Furthermore, all studies were based on the traditional TCD parameters such as mean flow velocity (MF), peak systolic flow velocity (PSF), end diastolic flow velocity (EDF) and PI (McCartney et al. 1997).

However, Schaafsma (2012) pointed out important theoretical drawbacks of these traditional TCD parameters. He defined an alternative set of TCD parameters, describing the systolic part of the blood flow velocity (FV) signal in more detail. Characteristics of this systolic part are the steep increase just after stroke onset, *acceleration* (acc), and two systolic peaks (sys1 and sys2). Sys1 and sys2 correspond to the A and B peak originally encountered in extracranial circulation (Baskett et al. 1977; Padayachee et al. 1982). This alternative set of parameters has theoretical and practical benefits but also, for instance, excellent discriminative power in a group of patients with ipsilateral carotid artery stenosis in comparison with normal controls (Schaafsma 2012).

Using this alternative set of TCD parameters, we aim to evaluate changes in cerebral hemodynamics in septic patients in comparison with healthy control subjects. To get more insight into the effects of fluid resuscitation on cerebral hemodynamics in sepsis, this study additionally aims to investigate whether this alternative set of TCD parameters can identify changes in cerebral hemodynamics after adequate fluid resuscitation in critically ill septic patients. Our hypothesis is based on the theory of arterial acceleration as forwarded by Schaafsma (2014). This theory assumes that the sys1 peak stems from a short-lasting contraction within the smooth muscle layers of the conducting arteries, elicited by the sudden increase in intra-luminal pressure at the onset of heart contraction. This contraction is assumed to spread throughout the arterial tree as a peristaltic wave to improve tissue perfusion throughout the body. In atrial fibrillation, it was observed that the sys1 peak was absent in heart beats with the smallest R-R' interval, suggesting there is either a threshold or a refractory period for the sys1 to occur. We hypothesized that in sepsis the threshold for a sys1 peak might not be reached, which would theoretically be detrimental for tissue perfusion. We used this hypothesis for the power calculation.

MATERIALS AND METHODS

A prospective observational study was conducted (March 2013–December 2014) at the Intensive Care Unit (ICU) of the Martini Ziekenhuis, Groningen, The Netherlands. The study protocol (registration number NL43415.099.13) was approved by the medical ethics committee (Regionale Toetsingscommissie Patiëntgebonden Onderzoek RTPO, Leeuwarden, The Netherlands) and was in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Informed consent was obtained afterward from relatives and whenever possible additionally from participating patients, according to the procedure of an emergency situation as stated in article 6, point 4 of the WMO Medical Research Involving Human Subjects Act (Ministerie van Buitenlandse Zaken, 1998).

Patients

We included adults (≥18 y) admitted to the ICU with a diagnosis of either severe sepsis or septic shock, according to standard international criteria (American College of Chest Physicians/Society of Critical Care Medicine 1992; Levy et al. 2003). In addition, patients needed to receive noradrenaline support and mechanical ventilation, and they needed to have a pulmonary artery catheter *in situ* that was used to guide fluid resuscitation. Patients were excluded if they had insufficient temporal windows for TCD investigation, had a life expectancy of <2 d at the moment of sepsis diagnosis, had an intra-cranial infection, had pre-existing brain injury or severe heart failure, were immune compromised or had no legal representatives available to give informed consent on behalf of the temporarily incapacitated patient.

On the basis of power analysis, we aimed to include a total of 16 patients in this study. Previous results from the study by Schaafsma (2012) were used for sample size calculation. A 2-sided sample size calculation with mean sys1-sys2 at the beginning of fluid resuscitation = −0.1, mean sys1-sys2 at the end of fluid resuscitation = 0.2, standard deviation (SD) = 0.2, $\alpha = 0.05$ and power = 0.80 determined that we needed to include a total number of 16 patients.

As a reference group, age- and gender-matched healthy controls were chosen from a larger pool of 42 patients described by Schaafsma (forthcoming). These were patients referred for tilt table testing because of transient loss of consciousness who had a normal response during