

ACTIVATION OF THE GLYMPHATIC SYSTEM DURING SLEEP – IS THE CEREBRAL VENOUS OUTFLOW A MISSING PIECE OF THE PUZZLE?

Marian Simka

Department of Anatomy, Faculty of Medicine, University of Opole, Opole, Poland

ABSTRACT

Until recently, mechanisms responsible for an activation of the glymphatic system of the brain, the system which is responsible for cleansing of this organ of waste products, were unclear. A recently published paper has finally shed some light on this problem. It has been demonstrated that there is a temporary decrease of the arterial cerebral blood flow during the deep phase of sleep, which is followed by an influx of the cerebrospinal fluid into the cranial cavity, and that this phenomenon is probably responsible for the activation of the glymphatic system. Although, of as yet, this issue has not been studied, it is likely that such a mechanism is not effective in the settings of disturbed cerebral venous outflow, and that in the case of venous congestion inside the cranial cavity, neurodegenerative lesions may develop. Therefore, the investigations on cerebral venous haemodynamics in the context of proper functioning of the glymphatic system should be one the directions of future research.

Key words: glymphatic system, chronic cerebrospinal venous insufficiency, internal jugular vein.

EDITORIAL PAPER

Phlebological Review 2019; 27, 1: 1–2
DOI: <https://doi.org/10.5114/pr.2019.93400>

Submitted: 4.02.2020

Accepted: 4.02.2020

ADDRESS FOR CORRESPONDENCE

Marian Simka
Department of Anatomy
Faculty of Medicine
University of Opole
11 A Kopernika Pl.
45-040 Opole, Poland
e-mail: mariansimka@poczta.onet.pl

Until recently, mechanisms responsible for activation of the astroglial-mediated interstitial fluid bulk flow, the so-called glymphatic system, were unclear, although it has been demonstrated that this system is primarily active during deep sleep [1–4]. Some researchers suggested that an increased pulsatility of the cerebral blood vessels could activate the glymphatic influx. However, the reason for this enhanced pulsatility, and why cerebral cleansing is more efficient during sleep, remained elusive. A recently published paper has finally shed some light on this problem [5]. It has been revealed that there is a temporary decrease of the cortical blood flow (measured by the BOLD fMRI) during the non-REM phase of sleep, which is followed by a macroscopic wave of inflow of the cerebrospinal fluid (CSF) at the level of the fourth ventricle. These haemodynamic and CSF flow oscillations are initiated by the slow-delta electrophysiological signalling.

Although during this study the function of the glymphatic system was not measured, it seems likely that aforementioned changes in the arterial and CSF flows are responsible for turning on the cerebral interstitial fluid bulk flow. Moreover, this important discovery suggests that an increased activity of the glymphatic system during deep sleep, which requires an enhanced flow of the CSF along the periarterial space surrounding the penetrating cerebral arteries, probably begins with the inflow of the

CSF into the cranial cavity from the vertebral canal, and that this inflow results from a decreased arterial volume inside the cranial cavity (the Kellie-Monroe doctrine). Such a mechanism would explain the need for sleep (at least regarding one of the functions of sleep). According to the results of the aforementioned study [5], an activation of the glymphatic system would require a temporary yet profound decrease in the activity of cortical neurons. Such a decrease would be difficult during the state of consciousness. However, in a deeply sleeping individual such coupled oscillations of the activity of neurons and the flow of the CSF would not interfere with physical activity or awareness.

In addition, the mechanisms of regulation of the activity of the glymphatic system, as suggested by Fultz *et al.* [5], would explain a possible role for impaired cerebral venous drainage in the pathophysiology of neurodegeneration. It has already been revealed that a pathology of veins draining the brain can be associated with a higher risk of neurodegenerative disorders. The glymphatic system is responsible for cleansing the cerebral parenchyma of waste products, and hence a higher risk of degeneration in the case of impaired glymphatic function [3, 6]. Taking into account the Kellie-Monroe doctrine, proper regulation of the activity of the glymphatic system would require an undisturbed venous outflow. Otherwise, during the phase of diminished arterial flow there would

be an increased pooling of venous blood inside the cranial cavity instead of the inflow of the CSF. Importantly, there are several reports linking an impaired cerebral venous outflow with neurodegenerative disorders [7-10], and papers demonstrating an association of an abnormal venous drainage with anomalous flow of the CSF [11-13]. Besides, it has already been suggested that abnormalities of the veins draining the brain, primarily lesions located extracranially, may be linked to neurodegeneration [14, 15]. Now, with the report by Fultz *et al.*, it seems easier to understand how such an abnormal venous outflow may result in neurodegenerative lesions of the brain. It might be speculated that in patients presenting with impaired cerebral venous drainage, because of such a compromised venous outflow, the oscillations of the cortical flow during the non-REM phase of sleep are not adequately accompanied by the changes of inflow of the CSF into the cranial cavity. This in turn would result in a less efficient cleansing of the brain parenchyma from pathological proteins, such as β -amyloid, α -synuclein, or β -synuclein, and in a higher risk of neurodegenerative disorders.

As yet, venous flows into and out of the cranial cavity have not been studied in this context. Therefore, considering the existing evidence, investigations on cerebral venous haemodynamics should be one the directions of future research.

The author declares no conflict of interest.

References

1. Benveniste H, Heerdt PM, Fontes M, et al. Glymphatic system function in relation to anesthesia and sleep states. *Anesth Analg* 2019; 128: 747-758.
2. Lee H, Xie L, Yu M, et al. The effect of body posture on brain glymphatic transport. *J Neurosci* 2015; 35: 11034-11044.
3. Plog BA, Nedergaard M. The glymphatic system in the CNS health and disease: past, present and future. *Annu Rev Pathol* 2018; 13: 379-394.
4. Hablitz LM, Vinitsky HS, Sun Q, et al. Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Sci Adv* 2019; 5: eaav5447.
5. Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* 2019; 366: 628-631.
6. Liguori C, Chiaravalloti A, Izzi F, et al. Sleep apneas may represent a reversible risk factor for amyloid- β pathology. *Brain* 2017; 140: e75.
7. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009; 80: 392-399.
8. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011; 77: 138-144.
9. Beggs C, Chung CP, Bergsland N, et al. Jugular venous reflux and brain parenchyma volumes in elderly patients with mild cognitive impairment and Alzheimer's disease. *BMC Neurology* 2013; 13: 157.
10. Chung CP, Beggs C, Wang PN, et al. Jugular venous reflux and white matter abnormalities in Alzheimer's disease: a pilot study. *J Alzheimers Dis* 2014; 39: 601-609.
11. Beggs CB, Magnano C, Shepherd SJ, et al. Aque ductal cerebrospinal fluid pulsatility in healthy individuals is affected by impaired cerebral venous drainage. *J Magn Imaging* 2014; 40: 1215-1222.
12. Beggs CB, Magnano C, Belov P, et al. Internal jugular vein cross-sectional area and cerebrospinal fluid pulsatility in the aqueduct of Sylvius: a comparative study between healthy subjects and multiple sclerosis patients. *PLoS One* 2016; 11: e0153960.
13. Beggs CB, Shepherd SJ, Cecconi P, Lagana M. Predicting the aque ductal cerebrospinal fluid pulse: a statistical approach. *Appl Sci* 2019; 9: 2131.
14. Simka M, Skuła M. Potential involvement of impaired venous outflow from the brain in neurodegeneration: lessons learned from the research on chronic cerebrospinal venous insufficiency. *Rev Recent Clin Trials* 2019; 14: 235-236.
15. Zivadinov R, Chung CP. Potential involvement of the extracranial venous system in central nervous system disorders and aging. *BMC Med* 2013; 11: 260.