This item is the archived peer-reviewed author-version of:

Do repetitive Valsalva maneuvers reduce glymphatic clearance?

Reference:

Wostyn Peter, Van Dam Debby, Audenaert Kurt, De Deyn Peter Paul.- Do repetitive Valsalva maneuvers reduce glymphatic clearance?
Annals of neurology - ISSN 0364-5134 - Hoboken, Wiley-blackwell, 81:2(2017), p. 322-322
Full text (Publisher's DOI): <https://doi.org/doi:10.1002/ANA.24851>
To cite this reference: <http://hdl.handle.net/10067/1406730151162165141>

Coversheet

Title of the article:

Do repetitive Valsalva maneuvers reduce glymphatic clearance?

Running head:

Valsalva maneuvers and glymphatic clearance

Full names:

Peter Wostyn, MD^{1,*}, Debby Van Dam, PhD^{2,3}, Kurt Audenaert, MD, PhD⁴, Peter Paul De Deyn, MD, PhD^{2,3,5}

Affiliations:

¹Department of Psychiatry, PC Sint-Amandus, Beernem, Belgium

²Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Department of Biomedical Sciences, Antwerp, Belgium

³Department of Neurology and Alzheimer Research Center, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

⁴Department of Psychiatry, Ghent University Hospital, Ghent, Belgium

⁵Department of Neurology and Memory Clinic, Middelheim General Hospital (ZNA), Antwerp, Belgium

***Corresponding author:**

Peter Wostyn

Department of Psychiatry, PC Sint-Amandus, Reigerlostraat 10, 8730 Beernem, Belgium

Phone: 32-472713719

Fax: 32-50-819720

E-mail address: wostyn.peter@skynet.be

Number of characters in the title:

61

Number of characters in the running head:

43

Number of words in the text.:

388

Number of figures, color figures, and tables:

0

Financial Support:

None

Conflict of Interest:

No conflicting relationship exists for any author

October 17, 2016

Dear Editor,

We read with great interest the paper recently published in *Annals of Neurology* by Ju et al¹ and would appreciate the opportunity to make a comment.

As discussed by the authors, several studies suggest that obstructive sleep apnea (OSA) may be a risk factor for Alzheimer's disease (AD).¹ To address the question of how OSA increases AD risk, they tested the hypothetical cascade of OSA causing increased arousals, decreased slow wave activity (SWA), increased synaptic activity and increased amyloid- β ($A\beta$).¹ Given that synaptic activity results in release of $A\beta$ from neurons, the authors hypothesized that $A\beta_{40}$ would be increased in OSA because of decreased SWA.¹ However, they unexpectedly found that cerebrospinal fluid (CSF) $A\beta_{40}$ was significantly decreased in the OSA group despite having lower SWA compared to controls.¹ The authors proposed glymphatic decline as one possible mechanism for the observed decrease in CSF $A\beta$ levels in OSA.¹ During an obstructive apnea, respiratory effort against a closed airway generates increased intrathoracic and intracranial pressure and a sudden pressure reversal at the end of the apnea.¹ As the intrathoracic pressure increases, veins distend increasingly due to reduced venous outflow from the brain, and peri-venous space closes resulting in diminished glymphatic system drainage of CSF into peri-venous space.² Therefore, repetitive high-pressure fluctuations may impede the glymphatic flow of $A\beta$ and other neuronally derived metabolites from interstitial fluid into CSF, resulting acutely in lower CSF concentrations.^{1,2}

If confirmed by further studies, it would be interesting to explore whether this mechanism can be observed also in individuals who frequently perform strong Valsalva maneuvers (VMs) (e.g., repetitive heavy lifting, playing a wind instrument, forceful and repetitive cough, ...),

and whether extensive use of the VM may increase the likelihood of AD development. The hypothesis of AD pathology resulting from CSF circulatory failure secondary to repetitive VMs has been previously suggested by our group.^{3,4} The VM is a forced expiration against a closed glottis, resulting in an increase in intrathoracic pressure and intra-abdominal pressure.⁴ With the rise in intrathoracic pressure, the thoracic vena cava is compressed, leading to reduced internal jugular venous return, and further causing an elevated intracranial venous pressure and subsequent elevated intracranial pressure.⁴ At least theoretically, the reduced venous outflow from the brain generated by repetitive VMs could lead to restriction of normal glymphatic flow and subsequent A β accumulation in the brain.

Sincerely yours,

Peter Wostyn, MD

Debby Van Dam, PhD

Kurt Audenaert, MD, PhD

Peter Paul De Deyn, MD, PhD

Potential Conflicts of Interest

The authors declare that they have no competing interests.

Authors' contributions

PW drafted and wrote the manuscript. DVD, KA and PPDD commented and revised the intellectual content of the manuscript. All authors have read and approved the final version of the manuscript.

References

1. Ju YE, Finn MB, Sutphen CL, et al. Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. *Ann Neurol* 2016;80:154-159.
2. Kiviniemi V, Wang X, Korhonen V, et al. Ultra-fast magnetic resonance encephalography of physiological brain activity – Glymphatic pulsation mechanisms? *J Cereb Blood Flow Metab* 2016;36:1033-1045.
3. Wostyn P. Can chronic increased intracranial pressure or exposure to repetitive intermittent intracranial pressure elevations raise your risk for Alzheimer's disease? *Med Hypotheses* 2004;62:925-930.
4. Wostyn P, Audenaert K, De Deyn PP. The Valsalva maneuver and Alzheimer's disease: Is there a link? *Curr Alzheimer Res* 2009;6:59-68.