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EDITORIAL - VASCULAR NEUROSURGERY - ANEURYSM

"Bucket" cerebrospinal fluid bulk flow: when the terrain disagrees with the map

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An invited Editorial [1] comments on a recent work where we used cardiac-gated phase-contrast magnetic resonance imaging (PC-MRI) to estimate net volumetric cerebrospinal fluid (CSF) flow rate in the cerebral aqueduct of individuals with cerebral aneurysms with or without a previous subarachnoid hemorrhage (SAH) [2]. The authors seemingly find daily CSF flow rates in the order of liters heavy to digest, particularly as they try to interpret the results in light of traditional concepts about CSF production and resorption.

First, we are indeed aware that PC-MRI has methodological weaknesses, which may become even more imminent by net CSF flow measurements. However, our main objective by reporting these data was to make the point that net CSF flow can occur in both directions through the cerebral aqueduct and in very different amounts in different patients. Even though the precision level of our results may be up for discussion, we can hardly see how the critique raised against our methodology changes the essence of the findings by order of magnitude and direction. The objections raised include too large slice thickness (5 mm), use of different scanners, long acquisition time (6 min) making results susceptible to respiration, and application of tailored VENC to measure high CSF flow velocities. We think otherwise; slice thickness of 5 mm (and in-plane resolution of 0.63×0.63 mm^2) is quite average [3] and should be acceptable at the aqueductal mid-level, where shape is close to being tubular. The fact that our findings are not machine-dependent should be considered a strength, not a weakness. Longer imaging duration renders for averaging out respiration effects, not increased influence. Correctly applied VENC for accurate measurements of high flow velocities in the center of the lumen should be preferred above aliased flow, as high flow contributes more to flow volume than slow flow in the periphery.

However, the main point being made in the Editorial [1] is simply that "bucket flow" does not fit into a model where CSF is produced exclusively by the choroid plexus within the ventricles and resorbed exclusively at the arachnoid villi at the brain surface. Harvey Cushing, by many considered as the father of modern neurosurgery, coined the term "the third circulation" in 1925 [4], in part based on the experiments by his contemporary, Walter E Dandy, who observed hydrocephalus after plugging the foramina of Monro in one single dog [5], and also the experiments by Lewis Weed [6], who had to proceed from small CSF tracers to avoid "diffuse tissue staining" within the brain to arrive at tracers large enough to accumulate solely at brain surface (reviewed by [7]). Since 1925, many lines of research have provided evidence that "the third circulation" represents a profound over-simplification for describing the pathways of CSF. It is, however, understandable that this model, attractive by its simplicity, and in which many scientists have invested much of their work, is hard to abandon.

Today, we know that the subarachnoid space is continuous with the perivascular and interstitial spaces of the entire brain and spinal cord, not only in animals [8–11], but also in humans [12, 13] (Fig. 1a). To and from the perivascular space, water molecules are continuously exchanged over the capillary wall [7],

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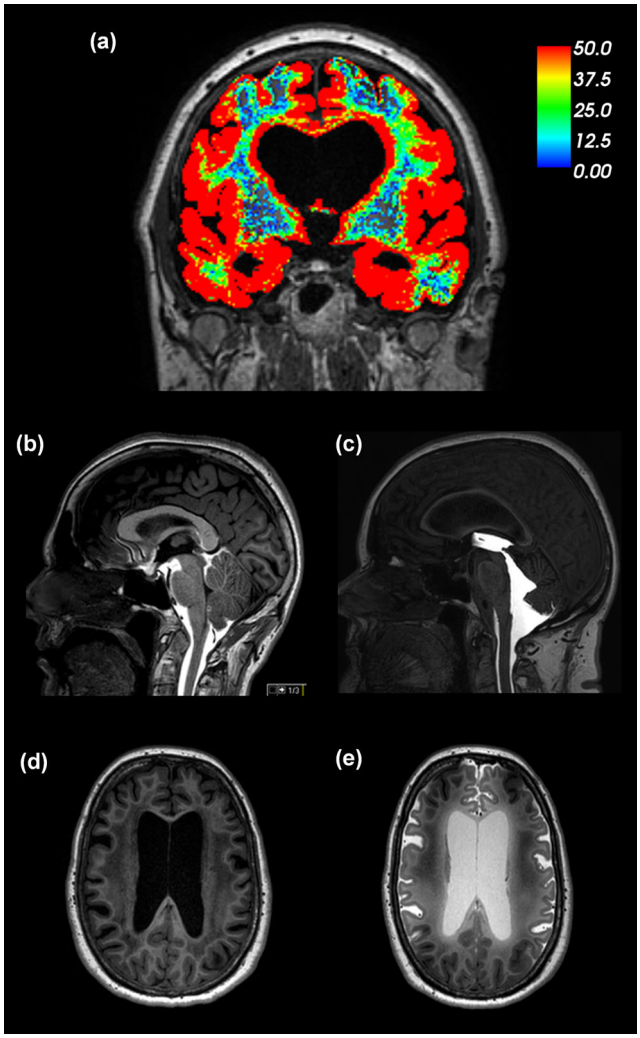

Fig. 1 The subarachnoid space communicates with the entire extravascular compartment of the human brain (**a**) and has been confirmed on cohort level in prospective studies [12–14]. The color scale illustrates percentage increase in normalized T1 signal intensity in brain of iNPH patient 24 h after intrathecally administered MRI contrast agent (gadobutrol) as CSF tracer. In contrast to normocephalic reference subjects (**b**), early and persistent CSF tracer reflux is a typical feature of hydrocephalic patients diagnosed with iNPH (**c**). Compared to pre contrast MRI (**d**), late scans obtained 24 h later demonstrate persistent ventricular tracer reflux (**a**) and enhancement of periventricular white matter (**a** and **e**)

which in human brain renders for a surface area for water exchange of up to 15–25 m^2 [15]. CSF and some of its molecular constituents are excreted to blood over the capillary wall, resorbed by true lymphatic vessels in the wall of dural sinuses [16, 17], and/or drained along lymphatic pathways through neuroforamina at the skull base [18]. In this respect, applying Davson's equation [19] to estimate to which extent all CSF is resorbed at the arachnoid villi must be considered an anachronism. That said, modeling studies demonstrated that the forces involved in aqueductal CSF flow are orders of magnitude smaller than those predicted by Davson's equation [20, 21].

Contrary to reference subjects (Fig. 1b), net retrograde aqueductal CSF flow in patients has been indicated by direct observations of early and persisting ventricular reflux of CSF tracer (intrathecal MRI contrast agent) [12, 13] (Fig. 1c). Ventricular tracer reflux precedes escape of tracer through the ventricular ependyma (Fig. 1a, d, e), even though the molecular size of tracer is far above that of water. In this sense, assuming that ventricular CSF would in its entirety be drained by an inserted tube appears as a logical shortcut.

A major issue of general interest in science is observations being put aside as flawed when not in line with a predefined model. Thereby, bias is introduced as the established model is exclusively receiving support. Science should rather be data-driven, not governed by hypotheses that are almost predefined as unalterable. According to the science philosopher Karl Popper (1902–1994), true progress in scientific knowledge goes through the method of falsification rather than verification, or "enlarging the graveyard of falsified hypotheses" (reviewed by [22]). This would, however, require both original and independent thinking.

References

1. Baledent O, Czosnyka Z, Czosnyka M (2018) "Bucket" cerebrospinal fluid bulk flow-is it a fact or a fiction? Acta Neurochir
2. Lindstrom EK, Ringstad G, Sorteberg A, Sorteberg W, Mardal KA, Eide PK (2018) Magnitude and direction of aqueductal cerebrospinal fluid flow: large variations in patients with intracranial aneurysms with or without a previous subarachnoid hemorrhage. Acta Neurochir
3. Ragunathan S, Pipe JG (2018) Radiofrequency saturation induced bias in aqueductal cerebrospinal fluid flow quantification obtained using two-dimensional cine phase contrast magnetic resonance imaging. Magn Reson Med 79:2067–2076
4. Cushing HW (1925) The third circulation and its channels. Studies in intracranial physiology and surgery: the third circulation, the hypophysics, the gliomas. H. Milford, Oxford university press Oxford, pp 1–51
5. Dandy WE (1919) Experimental hydrocephalus. Ann Surg 70:129–142
6. Weed LH (1914) Studies on cerebro-spinal fluid. No. III : the pathways of escape from the subarachnoid spaces with particular reference to the arachnoid villi. J Med Res 31:51–91
7. Brinker T, Stopa E, Morrison J, Klinge P (2014) A new look at cerebrospinal fluid circulation. Fluids and barriers of the CNS 11:10
8. Bedussi B, Almasian M, de Vos J, VanBavel E, Bakker EN (2017) Paravascular spaces at the brain surface: low resistance pathways for cerebrospinal fluid flow. J Cereb Blood Flow Metab: 271678x17737984
9. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Science translational medicine 4: 147ra111

10. Lam MA, Hemley SJ, Najafi E, Vella NGF, Bilston LE, Stoodley MA (2017) The ultrastructure of spinal cord perivascular spaces: implications for the circulation of cerebrospinal fluid. Sci Rep 7:12924
11. Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA (1985) Evidence for a "paravascular" fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Brain Res 326:47–63
12. Ringstad G, Valnes LM, Dale AM, Pripp AH, Vatnehol SS, Emblem KE, Mardal KA, Eide PK (2018) Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. JCI insight 3
13. Ringstad G, Vatnehol SAS, Eide PK (2017) Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain 140:2691–2705
14. Eide PK, Ringstad G (2018) Delayed clearance of cerebrospinal fluid tracer from entorhinal cortex in idiopathic normal pressure hydrocephalus: a glymphatic magnetic resonance imaging study. J Cereb Blood Flow Metab 271678X18760974
15. Wong AD, Ye M, Levy AF, Rothstein JD, Bergles DE, Searson PC (2013) The blood-brain barrier: an engineering perspective. Front Neuroeng 6:7
16. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K (2015) A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 212: 991–999
17. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. Nature 523:337–341
18. Ma Q, Ineichen BV, Detmar M, Proulx ST (2017) Outflow of cerebrospinal fluid is predominantly through lymphatic vessels and is reduced in aged mice. Nat Commun 8:1434
19. Davson H, Hollingsworth G, Segal MB (1970) The mechanism of drainage of the cerebrospinal fluid. Brain 93:665–678
20. Jacobson EE, Fletcher DF, Morgan MK, Johnston IH (1999) Computer modelling of the cerebrospinal fluid flow dynamics of aqueduct stenosis. Med Biol Eng Comput 37:59–63
21. Tangen KM, Hsu Y, Zhu DC, Linninger AA (2015) CNS wide simulation of flow resistance and drug transport due to spinal microanatomy. J Biomech 48:2144–2154
22. Hofmann B, Holm S (2015) Philosophy of science. In: Laake P, Benestad H, Olsen B (eds) Research in medical and biological sciences. Elsevier, Academic Press, pp 1–41