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RESEARCH

Hydraulic resistance of periarterial spaces in the brain

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CSF tracers are transported deeply into the brain via perivascular spaces [9–11].

The in vivo experimental methods of Mestre et al. [8] now enable measurements of the size and shape of the perivascular spaces, the motions of the arterial wall, and the flow velocity field in great detail. With these in vivo measurements, direct simulations can in principle predict the observed fluid flow by solving the Navier–Stokes (momentum) equation. These studies provide important steps in understanding the fluid dynamics of the entire glymphatic system [3, 12], not(],)aire

Fig. 1 Cross-sections of PASs from in vivo dye experiments. a We consider PASs in two regions: those adjacent to pial arteries and those adjacent to penetrating arteries. b the various shapes that are actually observed, or at least assumed. Here we propose the model shown in Fig. 2. This model consists of an annular channel whose cross-section is bounded by an inner circle, representing the outer wall of the artery, and an outer ellipse, representing the outer wall of the PAS. The radius of the circular artery and the semi-major axis (x-direction) and semi-minor axis (y-direction) of the ellipse can be varied to produce different cross-sectional shapes of the PAS. With , we have a circular annulus. Generally, for a pial artery, we have : the PAS is annular but elongated in the direction along the skull. For , the ellipse is tangent to the circle at the top and bottom, and for where is the dynamic viscosity of the CSF. (Note that the pressure gradient dp/dz is constant and negative, so the constant C we have defined here is positive.) If we introduce the nondimensional variables

then Eq. (1) becomes the nondimensional Poisson's equation domain corresponding to the part of the ellipse that does not overlap with the circle. We next specify the Dirichlet boundary condition flexible enough to be able to bend to one side of the circular orifice.) The increase of flow rate (decrease of resistance) is well illustrated in Fig. 3c–e, which show numerically computed velocity profiles (as color maps) at three different eccentricities. We refer to the outer ellipse too much makes the gaps narrow again, reducing the volume flow rate (increasing the hydraulic resistance). This results suggests that, for a given value of K (given cross-sectional area), there is an optimal value of the elongation that maximizes the volume flow rate (minimizes the hydraulic resistance).

To test this hypothesis, we computed the volume flow rate and hydraulic resistance as a function of the shape parameter for several values of the area ratio K. The results are plotted in Fig. 5a. Note that the plot is only shown for , since the curves are symmetric about . The left end of each curve ( ) corresponds to a circular annulus, and the black circles indicate the value of given by the analytical solution in Eq. (11). These values agree with the corresponding numerical solution to within 1%. The resistance varies smoothly as the outer elliptical bos(t)6(e t)6,6.3
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and the ellipse is highly elongated, while for large values of
K

are shown in Fig. 7b–d. Clearly the hydraulic resistances of the shapes observed in vivo are very close to the optimal values, but systematically shifted to slightly more elongated shapes. Even when differs substantially between the observed shapes and the optimal ones, the hydraulic resistance , which sets the pumping efficiency and is therefore the biologically important parameter, matches the optimal value quite closely.

Discussion

In order to understand the glymphatic system, and various effects on its operation, it will be very helpful to develop a predictive hydraulic model of CSF flow in the PASs. Such a model must take into account two important recent findings: (i) the PASs, as measured in vivo, are generally much larger than the size determined from post-fixation data [7, 8, 36] and hence offer much lower hydraulic resistance; and (ii) (as we demonstrate in this paper) the concentric circular annulus model is not a good geometric representation of an actual PAS, as it overestimates the hydraulic resistance. With these two factors accounted for, we can expect a hydraulic-network model to produce results in accordance with the actual bulk flow now observed directly in particle tracking experiments [7, 8].

The relatively simple, adjustable model of a PAS that we present here can be used as a basis for calculating the hydraulic resistance for a wide range of observed PAS shapes, throughout the brain and spinal cord. Our calculations demonstrate that accounting for PAS shape can reduce the hydraulic resistance by a factor as large as 6.45 (see Table tant r6186(an)9(t-33(ve)-13.8993(de)7d8(p)-1di including: (i) arterial pulsations drive CSF flow [8], and (ii) astrocyte endfeet, which form the outer boundary of the PAS, regulate molecular transport from both arteries and CSF [40, 41].

The configuration of PASs surrounding penetrating arteries in the cortex and striatum is largely unknown [42 scales as (b/ℓ) , where b is the amplitude of the wall wave and ℓ is the width of the gap between the inner and outer boundaries. Although this scaling was derived for an infinite domain, we expect it will also hold for one of finite length. For the case of a concentric circular annulus, the gap width ℓ and hence the pumping effectiveness are axisymmetric, and therefore the resulting flow is also axisymmetric. For an elliptical outer boundary, however, the gap width ℓ varies in the azimuthal direction and so will the pumping effectiveness. Hence, there will be pressure variations in the azimuthal direction that will drive a secondary, oscillatory flow in the azimuthal direction, and as a result the flow will be non-axisymmetric and the streamlines will wiggle in the azimuthal direction. Increasing the aspect ratio of the ellipse for a fixed area ratio will decrease the flow resistance but will also decrease the overall pumping efficiency, not only because more of the fluid is placed farther from the artery wall, but also, in cases where the PAS is split into two lobes, not all of the artery wall is involved in the pumping. Therefore, we expect that there will be an optimal aspect ratio of the outer ellipse that will produce the maximum mean flow rate due to perivascular pumping, and that this optimal ratio will be somewhat different from that which just produces the lowest hydraulic resistance. We speculate that evolutionary adaptation has produced shapes of actual periarterial spaces around proximal sections of main arteries that are nearly optimal in this sense.

Conclusions

Periarterial spaces, which are part of the glymphatic system [6], provide a route for rapid influx of cerebrospinal fluid into the brain and a pathway for the removal of metabolic wastes from the brain. In this study, we have introduced an elliptical annulus model that captures the shape of PASs more accurately than the circular annulus model that has been used in all prior modeling studies. We have demonstrated that for both the circular and elliptical annulus models, non-zero eccentricity (i.e., shifting the inner circular boundary off center) decreases the hydraulic resistance (increases the volume flow rate) for PASs. By adjusting the shape of the elliptical annulus with fixed PAS area and computing the hydraulic resistance, we found that there is an optimal PAS elongation for which the hydraulic resistance is minimized (the volume flow rate is maximized). We find that these optimal shapes closely resemble actual pial PASs observed in vivo, suggesting such shapes may be a result of evolutionary optimization.

The elliptical annulus model introduced here offers an improvement for future hydraulic network models of the glymphatic system, which may help reconcile the discrepancy between the small PAS flow speeds predicted by many models and the relatively large flow speeds recently measured in vivo [7, 8]. Our proposed modeling improvements can be used to obtain simple scaling laws, such as the power laws obtained for the tangent eccentric circular annulus in Fig. 3b or the optimal elliptical annulus in Fig. 5b.

Abbreviations

CSF: cerebrospinal fluid; PAS: periarterial space.

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Authors' contributions

JHT developed the theoretical ideas and the geometric model and outlined the calculations. JT and DHK carried out the calculations. HM and MN provided information on actual PAS shapes and flows. JHT, JT, and DHK analyzed the results and wrote the paper. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated and analyzed in the course of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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