Reviewer’s report

Title: A lumped model to calculate non invasively in clinical practice the brain outflow through collateral vessels

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Reviewer: Giovanni Malferrari

Reviewer’s report:

I read with great interest the paper proposed by Zamboni and coworkers and I think that the proposed model is attractive from a theoretical point of view, but several limitations raised from its practical applications. Some of these limitations have been signaled by the authors too.

I have general observations about the paper and some single point questions. The general observation first (Major Compulsory Revisions):

1. It is not clear how healthy subjects and patients were selected to limit biases
2. I think that the small sample size should not allow to make any valuable conclusion nor for healthy subjects and for patients, i.e. it is not possible to extend the findings from ten subjects to the entire burden of healthy people or diseased one. It is likely that healthy people can show a significant activation of the collateral outflow routes if the sample number increases and also diseased people could become a more heterogeneous group concerning the brain venous outflow
3. The p values of some measured and calculated parameters are very impressive (p < 0.000002) and it is hard to accept it in a such small cohort of subjects; moreover figures and tables show only CSA, TAV and in-outflow values, and therefore it is not easy to follow the reasoning of the authors step by step without reproducible analysis

Maybe a validation of the proposed model in a greater cohort of healthy subject would be desirable before to test the model in other situations and the use of another technique besides ultrasound technique to compare data and show the effective collateral activation would add methodological value to this work, whose founding idea is good and interesting.

Concerning the single point observations and questions:

1. IJV branches are always reported in the paper as re-entry channels, but they drains face and neck and also they may represent a component of a complex collateral network for brain drainage, therefore this last role is only one of the possibilities
2. Re-entry may be a misleading term, because it implies that the blood not only skips an IJV segment, but it can also flows more than one time in a local re-flow circuit, making very hard to assess the real flow volume, according to this hypothesis
3. The use of a fixed sample volume for TAV measurements on the venous side (for veins of different size) is associated to a consistent risk of missing low flow velocities, that more likely occur at the edge of the central flow lamina, and sometimes single flow laminae with inverted flow direction, making not assessable the reliability of TAV measurement in this context (Major Compulsory Revisions)

4. It is not clear if IJV CSA measurement has been performed by manually tracking the boundaries of the lumen or by using an automatic adjustable elliptic shape

5. Where VV outflow was calculated? V2 or V1 segment, referring to the correspondent artery segment?

6. It is not clear if and how much the CSA postprocessing refinement affect the final measurement: in all subjects? Only in subjects with a great breath variability?

7. The off line calculation of the insonation angle is not possible in the ultrasound platform, therefore it can be supposed that DICOM images were analyzed and measured with a DICOM viewer and TAV measurements without angle correction were used for the application of the formula. Is it correct?

8. The paper does not report the measure of angle correction and of the epsilon factor, although a great attention was paid to the relevant question of angle (Major Compulsory Revisions)

9. Measurements in J1 IJV segment are not easy and probably are not reliable (as the authors wrote), therefore it is not possible to build on them the interpretation of the findings (Major Compulsory Revisions)

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

No competing interest (My Institution received funding as one of the participating and tutoring centers for CoSMO study, sponsored by FISM, by this scientific foundation does not gain or loss in any way from the publication of this paper.)