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: Eva Bartels

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Major Compulsory Revisions - see attached pdf document:

Title: “A lumped model to calculate non invasively in clinical practice the brain outflow through collateral vessels”. “An ultrasound model to calculate the brain blood outflow through collateral vessels” would be a more adequate title.

Abstract

“Such evaluation is linked to a condition known as chronic cerebro-spinal venous insufficiency (CCSVI), characterized by some blockages in the IJV which are bypassed by collateral circulation, in turn activated to transport blood into the caval system”. This paragraph should be deleted, because: 1. Not relevant. 2. CCSVI is not a condition recognized by the medical community.

“We developed a novel lumped model to calculate the cerebral venous return, normalized to the arterial inflow, in the different segments of the IJV”. Drop the word “lumped”.

“Our preliminary application of the novel lumped model in the clinical setting suggests the pivotal role of the collateral network in draining the blood into the superior vena cava under CCSVI condition”. Drop the word “lumped”.

Background

There is general agreement in considering the internal jugular veins (IJVs) as the major route of cerebral outflow in the supine position, and the vertebral veins (VVs) as the major route of brain drainage in upright [1-4]. This true for most subjects but not for everybody. So your model should not disregard that small percentage of subjects who are exceptions to this rule.

Methods:

First phase of the study

“Total of eleven healthy volunteers were screened for CCSVI absence by means of established ECD criteria [5]. Ten out of eleven were enrolled in this phase (age ranging from 23 to 42 yo, male female ratio 6:4)”. Are you really sure that 10 subjects will suffice to build a universal model? I believe not. This is a major limitation of this study and the review process should end right here. Moreover, how did you select those 10 subjects: please detail all the inclusion and exclusion criteria. Was CCSVI the only exclusion criterium? Why was the eleventh healthy subject excluded?
Measurements were all performed in the morning hours following recommendation to drink 500 ml after the wake, in order to have comparable conditions of hydration. Please explain where you found that 500ml of any liquid will produce the same baseline condition of hydration. Please cite your references.

The vertebral artery (VA) was evaluated at V2 level. Please cite your references and explain why at this level and not at V3.

in the veins a smaller sample volume of 0.5 mm has been adopted. Sometimes, especially in the supine position, the blood rushes along the far wall of the vein. If a small sample volume is used and applied in the center of the vessel, the collected velocity data will be underestimated. Please explain how you managed to avoid this error. Also explain how you managed to collect accurate data from J1, where physiologically there is always turbulence.

“We carefully acquired the images and traces as above described, trying to improve as much as we could the reliability of the Doppler assessment and of the variables…”. Please explain how you improved the data collected and who made the corrections: a third author? Was he blinded?

“The acquisition phase was performed by two operators (FS and EM)”. What was the inter-observer agreement?

Phase two of the study

“We tested our model on a second population represented by ten patients (age ranging from 37 to 45 yo, male to female ratio 5:5) affected by CCSVI…”. Only 10 patients were recruited to test your model? This is another major limitation of this study. How did you select those 10 patients? Please detail all the inclusion and exclusion criteria. It is obviously not enough to say they all had CCSVI.

Results

First phase of the study

Arterial inflow

“The control subjects were successfully investigated. Measured CCAs flow was 836 167 ml/min, subdivided in 464 74 ml/min in the ICs, 226 59 ml/min in the ECs…” CCAs flow is greater than ICAs+ECAs flow: explain.

Venous outflow in upright posture

“In Table 1 we report CSA, major axis, TAV, and Q respectively for left and right IJV, measured in sitting; TAV increases from J3 to J1, whereas CSA and major axis are apparently constant.

In our sample the rate of HBinF drained by the IJVs is 26% in J3, 33% in J2 and more than 90% in J1, respectively, and thus suggesting, also in upright, a re-entry of significant volume of blood along the course of the jugular vein through the collaterals”. Explain how it is possible that more than 90% of HBinF is drained by the IJVs in upright posture? Aren’t the VVs the main draining route in this position?

Second phase of the study
Same questions as for first phase of the study.

Comparison in upright position

By turning the subjects in sitting posture, we did not find out significant differences between patients and controls. Explain these results.

Conclusion

“…The preliminary application of the model seems to indicate how a significant rate of the head inflow is drained by the collateral network rather than by the IJV in the CCSVI condition…”. This is not a surprise at all, actually it is well expected since all your patients, as you have mentioned in the methods section, had an intraluminal IJV flow obstruction. However, this model cannot be generalized to all CCSVI patients (i.e. those not having a positivity for criterion 3).

This paper does not meet the minimum requirements for publication:
1. the study sample is too small to build a universal model.
2. the patient sample is too small to infer anything.
3. the patient sample does not represent the CCSVI patient population, consequently the study results cannot be generalized to the CCSVI population.
4. this paper needs major language editing.

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests