# Reproducibility of Venous Luminography and Flow Quantification Related to the CCSVI Hypothesis

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**Background:** Chronic cerebrospinal venous insufficiency (CCSVI) is a recent hypothesis by Zamboni et al. that reflux to the level of the deep cerebral veins induces amplified iron deposition and a neuroinflammatory cascade of events that ultimately result in Multiple Sclerosis (MS). It has generated much interest in the visualization and quantification of venous blood flow using various imaging techniques. Zamboni proposed 5 ultrasound (US) [1] based criteria of diameter changes and impaired flow in the cerebrospinal veins to diagnose MS. While possessing a high temporal resolution and flow feedback, US exams are highly user dependent and may not effectively blind the examiner to the condition of the patient. MR which is user independent, allows for easy blinding, and can provide whole vessel coverage is better suited for such measurements. However, MR flow imaging and MR angiography concentrates almost exclusively on the imaging of arteries.. It is known that flow through the jugular veins is extremely variable, changing with head tilt, posture, respiratory cycle, and even hydration. Also, quantitative vessel diameter assessments and identification of stenoses in veins are notoriously difficult are not part of clinical diagnosis. Thus the accuracy and reproducibility of MR venous flow assessment with phase contrast (PC) and vessel assessment with contrast-enhanced (CE) MRA is unknown. To test the repeatability of venous flow quantification, a 4D MR Flow approach, PC-VIPR [2], was adopted for venous flow measurements and subjected to an in-vivo test-retest reliability study. The purpose of this study is to internally validate, both qualitatively and quantitatively, the use of PC-VIPR and CE-MRA to assess cerebrospinal blood flow and lumen changes in testing the CCSVI hypothesis.

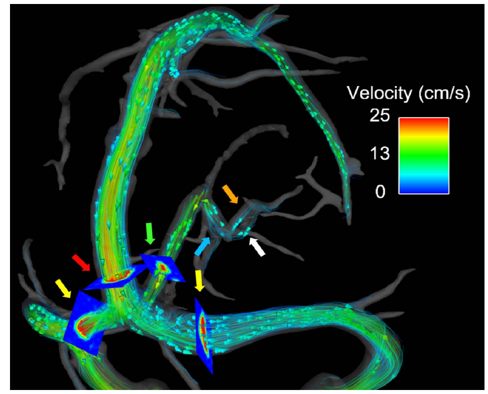
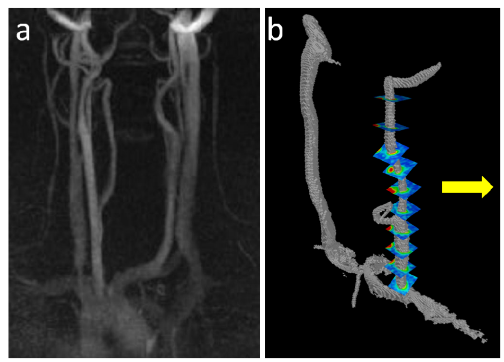



*Figure 1 Example flow visualization for COM. Arrows: yellow – left/right transverse sinus, red – sagittal sinus, green – straight sinus, blue – vein of Galen, internal cerebral veins – left (orange), right (white). Planes mark location of flow measurement.*

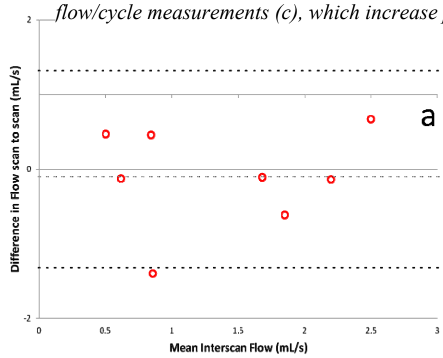
**Methods:** Eight healthy volunteers (38.1±15.0 years, 81.3±15.4kg, 3M, 5F) were imaged on a clinical 3T system (Discovery MR750, GE Healthcare, Waukesha, WI) after obtaining IRB approval and written informed consent. Each volunteer was imaged twice within two weeks (8 volunteers x 2 = 16 total scans) at three different stations: the cerebral veins (head), the neck veins, and the chest (azygous vein). Parameters for the head scan included: Dual echo, FOV: 24 x 24 x 16 cm, acquired spatial res: $(0.6\ mm)^3$, 9000 projections (36x undersampled), TR=15.9 ms, BW=31.25 kHz, VENC=20 cm/s, 7:30 min scan time. Parameters for the neck and chest scan were similar, with a higher VENC for the neck and a larger FOV for the chest. Cardiac triggers were recorded for retrospective cardiac gating with additional modifications being investigated for retrospective double-gated cardiac and respiratory reconstruction to address respiratory effects in venous flow. A single injection of gadofosveset trisodium (Ablavar, Lantheus Medical Imaging, N. Billerica, MA) with 0.03-0.05 mmol/kg at 3 ml/s was used for a first pass perfusion scan, contrast-enhanced MRA, and subsequently for the PC-VIPR scans. The image sets were segmented and exported to an advanced visualization software package (EnSight, CEI, NC). The flow data could then be measured [3] using arbitrarily oriented planes placed orthogonally to the direction of flow. To test data consistency, a "conservation of mass" (COM) approach was used at the torcular herophili, which marks the confluence of flow (Q) entering from the superior sagittal sinus and straight sinuses, and exiting via the bilateral transverse sinuses: $Q_{Superior\ Sagittal} + Q_{Straight\ Sinus} = Q_{Right\ Transverse} + Q_{Left\ Transverse}$ (Fig. 1). These results were subjected to Bland-Altman analysis. In the internal jugular vein (IJV), to compare total flow over the cardiac cycle from one scan to the next for a given volunteer, ten evenly spaced planes were placed down the (IJV) from the jugular bulb to the jugular-subclavian junction (Fig. 2b). This allowed for direct comparison of flow for each plane in a test-retest fashion. Two markers for repeatability were examined, the peak flow and total flow over the cardiac cycle. To assess if the cerebrospinal veins were positive for reflux (a main condition for the diagnosis of CCSVI), the percent retrograde flow was calculated as the integrated negative flow (away from the heart in veins) divided by the total integrated flow for the following vessels: basal veins of Rosenthal, internal cerebral veins (averaged over left and right), vein of Galen, straight sinus, and the azygous vein. Finally to assess the reproducibility of anatomical assessments, CE-MRAs were scored by two experienced, blinded radiologists for ability to assess the IJV and azygous vein (1-poor, 2-acceptable, 3-good, 4-excellent), azygous vein morphology (1-diffusely irregular/narrowed, 2-focally narrowed at central aspect, 3-caliber increasing from peripheral to central), and IJV morphology narrowest point (1-absent, 2-pinpoint, 3-flattened, 4-crescentic, 5-ellipsoidal/round) [5].




c

| Plane | Total Flow (mL/s) |
|---|---|
| 1 | 1.26 |
| 2 | 0.97 |
| 3 | 0.63 |
| 4 | 0.96 |
| 5 | 0.79 |
| 6 | 0.84 |
| 7 | 2.63 |
| 8 | 1.77 |
| 9 | 2.76 |
| 10 | 2.87 |
| Average | 1.55 |

*Figure 2 Coronal MIP (a) shows good quality PC VIPR angiograms carotid arteries and IJVs. Planes (b) placed down the left IJV yield total flow/cycle measurements (c), which increase proximal to the heart.*




b

| | |
|---|---|
| Galen | 0.75 |
| Rosenthal | 1.92 |
| Internal Cerebral | 1.52 |
| Straight Sinus | 3.42 |
| Azygous Vein | 5.51 |

c

| | Scoring Difference Rad 1 | Rad 2 | Mean ± StDev |
|---|---|---|---|
| IJV Image Quality | 0.25 | 0.5 | 3.6 ± 0.6 |
| Left IJV Morphology | 0 | 0.13 | 3.0 ± 1.1 |
| Right IJV Morphology | 0.5 | 0.38 | 3.7 ± 1.3 |
| Azygous Vein Image Quality | 0.75 | 0.63 | 3.0 ± 0.9 |
| Azygous Morphology | 0.25 | 0.38 | 2.9 ± 0.2 |

*Figure 1 Summary of data analysis.*

**Results:** Results for the COM analysis are shown in Fig. 3a. The Bland-Altman plot demonstrates that all but one result are within the coefficients of repeatability, and are slightly biased. This is confirmed by calculating the difference at the torcular herophili for each scan and the percent difference between scans, yielding an average value of 5.6%. The results of the IJV analysis demonstrate large variations in total flow. The average percent difference in peak flow between scans through the cardiac cycle across all planes and volunteers was 8.6%, while the same metric used for the total flow over the cardiac cycle was considerably higher, at 20.7%. Percent retrograde flow for deep cerebral veins and the azygous vein is shown in Fig. 3b. Scoring results from the CE-MRA are listed in Fig. 3c.

**Discussion and Conclusions:** A novel phase-contrast protocol developed specifically for venous flow quantification was implemented and assessed for reproducibility in healthy volunteers. Within roughly 5%, COM held true for internal validation at the torcular herophili and demonstrated the use of PC-VIPR for flow quantification in deep cerebral veins. High interscan variability in IJV flow was observed, indicating the need for careful controlling of variables impacting venous flow in CCSVI research. Retrograde flow percentages in deep cerebral veins where reflux has been reported in MS patients [1] very near zero as expected for normal volunteers. Data suggests that some reflux in the azygous vein may be normal. CE-MRAs produced no significant differences between blinded scoring, indicating repeatability of qualitative anatomical venous assessments.

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**References:** [1] Zamboni, P. *JNNP* (2009). [2] Gu, T. *AJNR* (2005). [3] Stalder, A. F. *MRM* (2008). [5] Zivadinov, R. *Neurology* (2011).