**Internal jugular vein cross-sectional area and cerebrospinal fluid pulsatility in the aqueduct of Sylvius**

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**Background:** Constricted cerebral venous outflow has been linked with increased aqueductal CSF pulsatility in healthy individuals [1] and MS patients [2]. However, the relationship between the CSF pulsatility and internal jugular vein (IJV) cross-sectional area (CSA) is unknown.

**Objective:** To characterise links between IJV CSA and aqueductal CSF pulsatility in MS patients and healthy subjects.

**Methods:** 98 relapsing-remitting MS patients (62 males and 36 females; mean age=44.2 years) and 99 healthy controls (48 males and 51 females; mean age=43.9 years) were investigated. CSF flow quantification involved cine phase-contrast MRI, while IJV CSA was calculated using magnetic resonance venography. Cardiovascular risk factor data were collected. Statistical analysis involved correlation, and partial least squares correlation (PLSC), analysis [3].

**Results:** For healthy controls, PLSC revealed a significant relationship (p=0.001) between CSF pulsatility and IJV CSA in the lower neck (C5-C7), and a trend for this relationship (p=0.091) at C2-C4. PLSC revealed no relationships in MS patients. After controlling for age and cardiovascular risk factors, many significant correlations were identified in the healthy controls between the CSF and IJV variables [e.g. net positive CSF flow and left IJV CSA at: C7-T1 (r=0.416, p=0.002) and C5-C6 (r=0.389, p=0.003); and net negative CSF flow and left IJV CSA at: C7-T1 (r=-0.352, p=0.008) and C5-C6 (r=-0.349, p=0.009)], whereas there were only two significant correlations in MS patients [i.e. net positive CSF flow and right IJV CSA at: C5-C6 (r=0.311, p=0.035) and C4 (r=0.298, p=0.047)].

**Conclusions:** In healthy adults, higher aqueductal CSF pulsatility is correlated with increased IJV CSA (particularly in the lower neck) in a relationship independent of age and cardiovascular risk factors. This relationship is largely absent in MS patients. Given CSF pulsatility and venous drainage are linked in healthy individuals [1], it may be that increased IJV CSA is indicative of stasis in venous outflow.

(Word count = 300 words)

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**Blood storage within the intracranial space and its impact on cerebrospinal fluid dynamics**

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**Background:** The volumetric changes that occur throughout the cardiac cycle (CC) in the various intracranial vascular compartments are poorly understood. Although blood entering/leaving the cranium is pulsatile, flow in the cerebral vascular bed is non-pulsatile [1], implying the transient storage of blood.

**Objective:** To characterise the temporal changes in fluid volume that occur within the cranium throughout the CC.

**Methods:** Neck MRI data were acquired from 14 healthy adults (age <35), using a 1.5 Tesla scanner. Arterial, venous and cerebrospinal fluid (CSF) flow rate data acquired at the C2/C3 level were standardized to 32 points over the CC. The relative changes in the intracranial arterial, venous and CSF volumes were calculated by: (i) integrating the respective flow rate signals to compute the instantaneous volumetric changes (*ivc*); (ii) mean centering the respective *ivc* signals; and (iii) cumulating the mean centered *ivc* signals to yield the fluid volumetric changes in the cranium throughout the CC.

**Results:** The aggregated flow rate signals for all subjects are shown in Figure 1, while Figure 2 shows the relative changes in the intracranial arterial, venous and CSF volumes. A strong inverse relationship exists between the arterial and venous volumetric signals ($r = -0.844$, $p<0.001$). As the intracranial arterial blood volume decreases to a minimum during diastole, so blood is stored in the intracranial venous compartments. This coincides with the period when the intracranial CSF volume increases. Only when the intracranial CSF volume peaks and starts to decrease, is the venous blood stored in the cranium allowed to discharge.

**Conclusions:** The behavior of the venous pulse is controlled by volumetric changes within the cranium in a process that is mediated by the CSF. This finding supports the hypothesis that CSF interacts with the cortical bridging veins to facilitate the storage of venous blood during diastole [2,3].

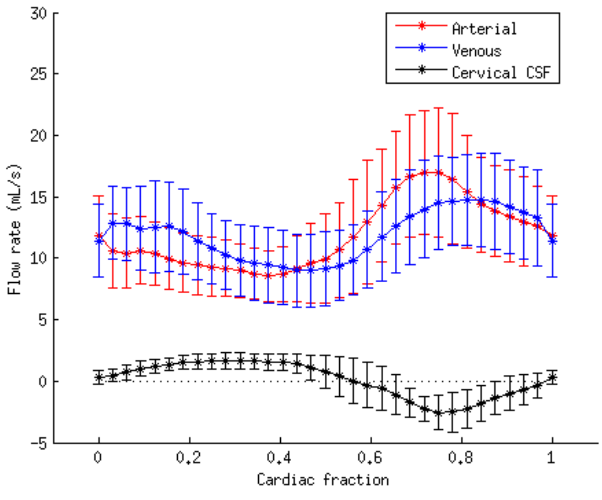


Figure 1. Aggregated fluid flow rates.

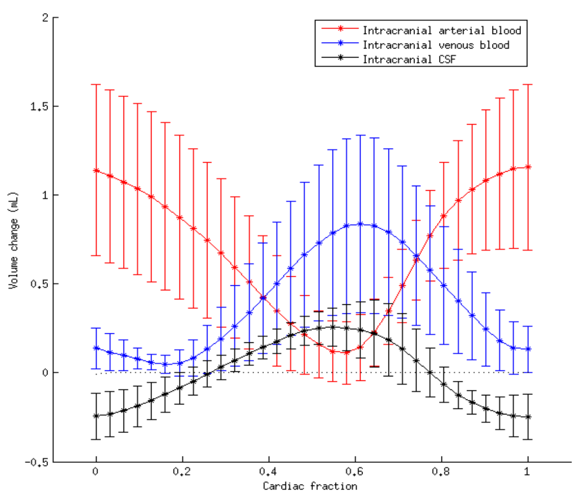


Figure 2. Relative intracranial fluid volumes.

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# CEREBRAL CIRCULATION IN PATIENTS WITH MULTIPLE SCLEROSIS. A COLOR-DOPPLER STUDY OF EXTRACRANIAL ARTERIAL AND VENOUS VESSELS.

Amedeo Cervo, Maria Grazia Caprio, Monica Ragucci, Marcello Mancini

## BACKGROUND

Recent studies hypothesized Multiple Sclerosis (MS) to be influenced by alterations of cerebral circulation.

## OBJECTIVES

To assess whether there is a relation between MS and cerebral circulation, by quantifying arterial inflow and venous outflow and by measuring carotid wall intima–media thickness (IMT).

## METHODS

82 MS patients and 53 healthy controls (HC) underwent to extracranial color-Doppler examination in supine and upright for analysis of arterial and venous blood volume flow. Internal Carotid Artery (ICA) was determined 1.5 cm away from the carotid bifurcation. Vertebral artery (VA) was examined in the V2-segment. Cerebral Blood Flow (CBF) was calculated as the sum of flow volumes in both ICA and VA. Mean intima–media thickness (IMT) was measured over a segment of the common carotid artery. Cross-sectional areas of J1, J2 and J3 tracts of IJVs and venous blood flow in the J3 tract of IJV and in the most caudal tract of VV were measured.

## RESULTS

The MS group showed lower IJV blood flow than HC in supine position (258.1 ml/m vs 327.7 ml/m; p=0.025). No difference was found in the VVs flow. No parameters in the upright position were different. No difference was found in prevalence of IJV stenosis between the two groups. No differences between groups were seen in arterial inflow (CBF MS mean and range: 597.7ml, 400.2-821ml, HC 561.7ml, 242,2-896.7ml p 0.055) and IMT (MS 0.54mm, 0.42-0.92mm, HC 0.49mm, 0.4-1.09mm; p 0.033).

## CONCLUSIONS

The results indicate an association between abnormal cerebral venous flow and MS. No differences between MS and HC in CBF and carotid IMT were detected.

## KEYWORDS

Multiple Sclerosis; Internal Jugular Vein; Cerebral Blood Flow; Carotid; IMT; Echo-Color Doppler Ultrasonography.

## ABNORMAL CORTICAL SOURCES OF RESTING STATE EEG RHYTHMS ARE RELATED TO INTERNAL JUGULAR VEINS FLOW IN RELAPSING-REMITTING PATIENTS WITH CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY

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**Background.** Some patients with multiple sclerosis (MS) suffer from chronic cerebrospinal venous insufficiency (CCSVI) due to stenosis or malformations of neck veins including internal jugular ones (IJVs). Unfortunately, it is unclear the relationship between such cerebro-vascular abnormality and brain function.
**Objectives.** Here we tested the hypothesis that CCSVI within IJV is related to an abnormal brain function as revealed by cortical sources of resting state electroencephalographic (EEG) rhythms in relapsing–remitting (RR)-MS subjects.
**Methods.** Resting state eyes-closed EEG rhythms were recorded in 50 RR-MS patients with CCSVI and in 50 matched healthy control (HC) subjects. IJV blood empting time estimated CCSVI in the MS patients during angiography. Based on the median of the IJV blood empting time, the RR-MS subjects were divided into a CCSVI- group (lowest degrees of CCSVI; N=24) and a CCSVI+ group (highest degrees of CCSVI; N=26). EEG rhythms of interest were delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10.5-13 Hz), beta 1 (13-20 Hz), and beta 2 (20-30 Hz). LORETA freeware estimated the cortical EEG sources.
**Results.** Compared to the control group, the RR-MS group showed an amplitude decrease of widespread alpha 1 cortical sources and an amplitude increase of parietal delta cortical sources. In the RR-MS group, the amplitude of widespread alpha cortical sources was lower in the CCSVI+ group compared to the CCSVI- group.
**Conclusion.** The present results suggest that CCSVI is related to widespread cortical sources of resting state alpha rhythms in the RR-MS group. Future studies will investigate whether such relationship is specific for the RR-MS group compared to control groups of healthy and neurological subjects.

**Keywords**: Multiple sclerosis (MS), Relapsing-Remitting (RR), chronic cerebrospinal venous insufficiency (CCSVI), Electroencephalography (EEG), Low-resolution brain electromagnetic tomography (LORETA).

# Impact of incompetence and obstruction of valves in internal jungular veins on intracranial venous haemodynamics: a computational study

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**Background:** Anomalies in extracranial venous vessels have recently been linked to potential cerebral venous hypertension and this, in turn, to neurodegenerative pathologies. Unfortunately, confirmation of intracranial venous hypertension through invasive methods, or other measuring techniques, is currently unavailable. Alternatively, computation offers nowadays the possibility of quantifying brain haemodynamics. Extracranial venous anomalies cover a wide range of vessels and abnormalities, including stenosis and valve malfunction. Here we are concerned with valves in internal jugular veins (IJVs) in subject in supine position under regular breathing.

**Objectives:** To quantify, by means of a mathematical model, the impact of IJVs valves competence and obstructions on cerebral venous haemodynamics.

**Methods:** We use a recently constructed global mathematical model for the human circulation that has been validated against in vivo MRI data. Nine sets of simulations for subjects in supine position were performed, by considering varying degrees of valve incompetence and obstruction.

**Results:** High degrees of valve incompetence and obstruction show an increase of intracranial venous pressure and reflux. The effect of incompetence and obstruction of up to 60% is small, while obstructions greater than about 60% produce sharp increases of pressure. In particular, total obstruction of valves gives pressure changes in SSS of +2.2 mm Hg (+29,7%) and the flow is redirected to other veins, such as EJVs (+4.8 ml/s, +480%).

**Conclusions:** While valve incompetence for subjects in supine position and regular breathing shows little effect on brain haemodynamics, severe valve obstruction produces sharp increases of pressure in deep cerebral veins and highly disturbed venous return. These results could be significantly modified under change of posture or respiratory maneuvers, such as Valsalva.

***Keywords:*** *Cerebral Venous Haemodynamics – Intracranial venous hypertension - Mathematical modelling - Valves in IJVs - Neurodegenerative Diseases.*

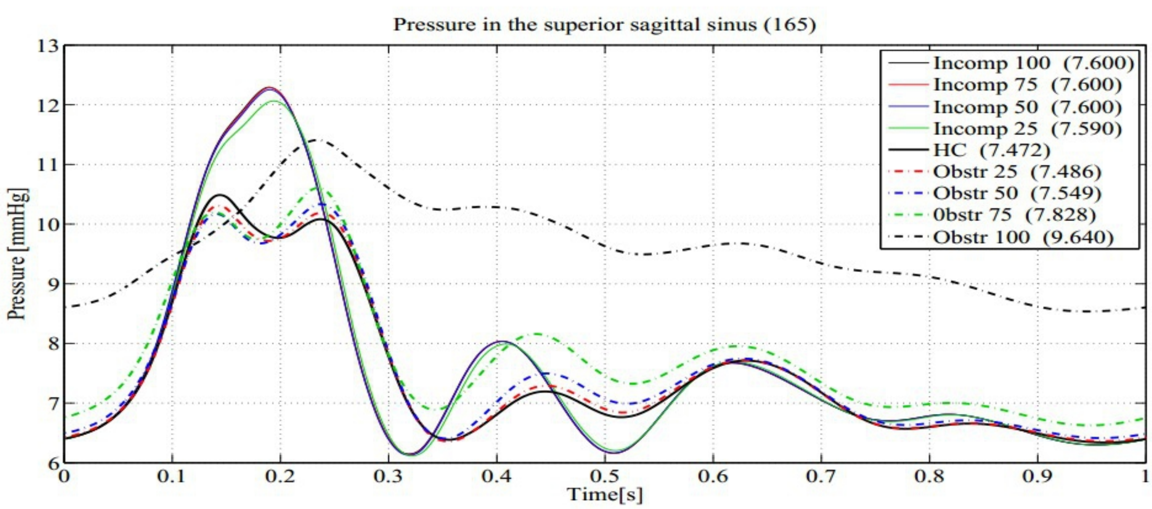


**Fig.1** Pressure in the SSS, for an healthy control case (HC) and for different degrees of obstruction (Obstr) and incompetence (Incomp) of valves in IJVs.

Ultrasound-guided surgical procedure for Internal and External Jugular veins occlusion in mice: preliminary results.

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Introduction

The relationship between venous abnormalities and neurological diseases are not widely investigated. Only few studies explored the venous involvement in such diseases. Some studies show that in mice there are multiple connections between intracranial veins and external jugular veins (EJV). Therefore the venous circulation of mouse brain, unlike humans, has two different routes runoff formed by the internal jugular vein (IJV) and EJV. Aim of our study was to develop a mice model of cerebral outflow occlusion in order to assess the correlations between venous stasis and the development of neurological diseases. At this purpose, we used high frequency ultrasound (HFUS) to assess the feasibility of electrocoagulation to obtain neck veins occlusion in mice.

Methods

Fourteen C57/black, female, five weeks old mice were used for this study. 4 mice underwent to bilateral occlusion of the IJV, 4 mice underwent to bilateral occlusion of the EJV, 4 both of the EJV and IJV and 2 mice were used as controls (sham operated mice). All the procedures were performed under general anesthesia with Isoflurane (2%) in 100% oxygen at 0.8 L/min. Blood venous flow of JVs was evaluated before and after surgical procedure by Color Doppler HFUS (Vevo 2100, Visualsonics) with a 40 MHz probe. A ventral midline stab incision was performed on the neck to access the EJV. Deeper blunt dissection was completed, on each side of the trachea, to expose the IJV. An electro-surgical equipment (DIATERMO MB 160, GIMA spa), mounting a small electrode for monopolar coagulation, was used to induce venous occlusion. Skin was closed with 6-0 Vicryl (Johnson&Johnson Medical spa) in a simple continuous pattern and a triple antibiotic ointment was applied over the incision. Sham operated mice were not subjected to electrocoagulation. All procedures where approved by ethical committee and supervised by a Veterinary Doctor.

**Results**

Two of fourteen mice underwent to pulmonary complications during the surgical procedure, therefore the mortality was of 14%. The IJV and EJV were well identified with color Doppler HFUS prior (fig. 1A) and after the surgical procedure (fig. 1B). In all cases examined, HFUS allowed us to confirm the absence of flow in the obstructed veins after the electro-coagulation procedure. All survivors are under neurological examination to assess the brain damage secondary to neck veins occlusions.

**Conclusions**

In our study, we evaluated the feasibility of ultrasound-guided surgical procedure that resulted a procedure with low mortality and efficacy in 100% of survivors. As the neck mouse veins anatomy is not similar to human, in vivo imaging of normal neck vessels is necessary for the evaluation of animal models. Further studies are in progress to evaluate brain damage secondary to the occlusion of extracranial veins in mice.

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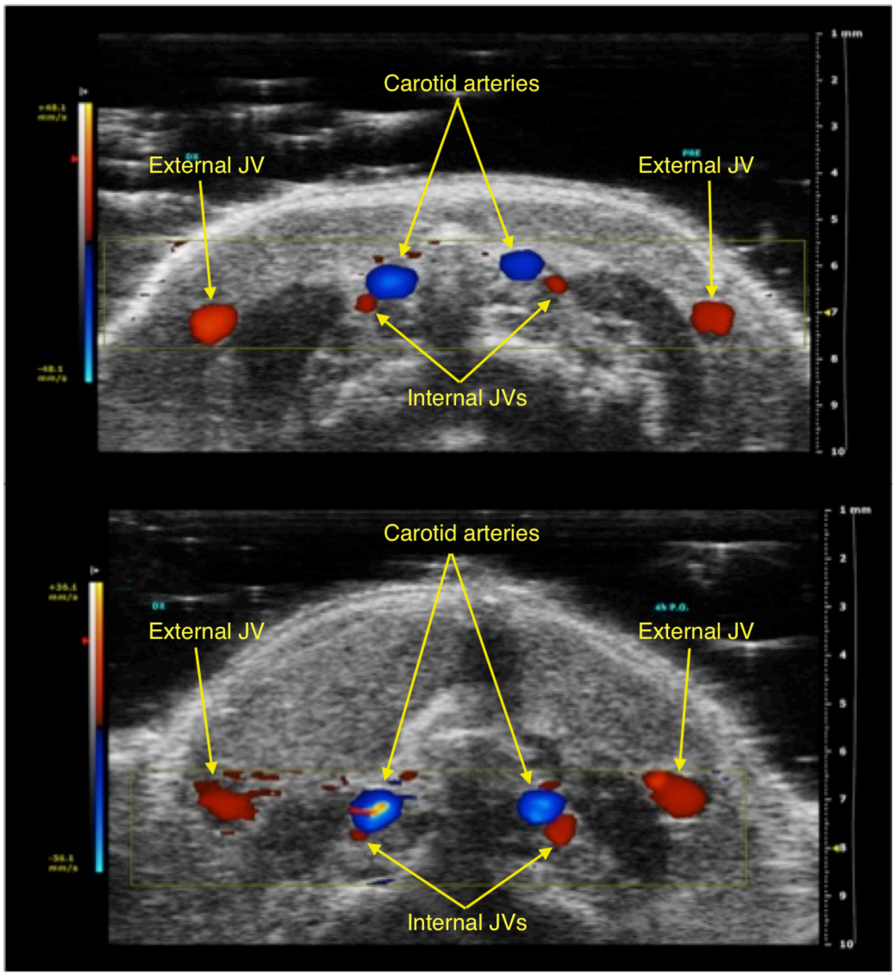
Figure 1: Images of Doppler High Frequency Ultrasound of neck vessels in normal mice (A) and in sham operated mice (B). See shadow back due to surgical suture (B).

Figure 1



**Disturbed intracranial venous haemodynamics and macromolecule transport across vessel walls: a mathematical model.**

Eleuterio Toro, Laura Facchini and Alberto Bellin

**Background.** The recent association of extracranial venous strictures to Multiple Sclerosis [1] has posed a number of partly unresolved hypothesis, one of them being intracranial disturbed flow and venous hypertension. By means of a global mathematical model for the human circulation [2] it has been found that intracranial flow disturbances and venous hypertension are possible. Another step in the chain of events leading to MS, involves increased permeability of the BBB due to altered venous haemodynamics and potential transport of colloids from the vessel lumen to the brain tissue. It is desirable to construct a mathematical model that addresses this issue; preliminary results are given in [3].

**Objectives.** To describe a simple mathematical model for plasma and molecule transport across blood vessel walls and perform a parametric study to identify biophysical quantities that affect vessel wall permeability and transport.

**Methods.** We use a mathematical model to study the consequences of brain venous hypertension regarding macromolecule transport across vessel walls.

**Results.** We studied the effect of three parameters (1) glycocalyx degradation, (2) local hydrostatic pressure and (3) increase in pore number and/or radius. Our results show that an increase in each of these three parameters results in increased plasma filtration and/or solute extravasation, as one would have expected.

**Discussion and conclusions.** Mathematical modelling is helping in elucidating recently proposed medical hypotheses based on the empirical observation of a strong association between MS and extracranial venous strictures. Computational quantification supports the plausibility of the proposed chain of events: extracranial venous strictures, disturbed intracranial venous flow, venous hypertension, increased plasma filtration and/or solute extravasation. More research is needed.

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**Multiparametric automated segmentation of brain veins**

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**Background:** Manual segmentation of brain vessels in a typical MR dataset is both complex and time-consuming; therefore automated approaches are actively sought for, as they also improve the reproducibility of the results.

**Objectives:** To present a multiparametric segmentation method (MPS) that, starting from a vessel likeliness function (Vesselness) and R2* map of the brain, applies an Expectation Maximization (EM) algorithm to the bivariate distribution of the data to classify each voxel as belonging or not to veins.

**Methods:** Based on the assumption that a voxel belonging to a vein has high Vesselness and R2* values, on the log-scale joint histogram of the maps, the voxels whose Vesselness is higher than 0 were assigned to 3 main classes: 1. a Gaussian distribution with low R2* and Vesselness (false positives enhanced by Vesselness), 2. a class with R2* value above a given threshold, 3. another Gaussian distribution with medium-high value of R2* and high value of Vesselness, the last two truly corresponding to veins. Through an EM algorithm, the parameters of the 3 classes were estimated and the voxels belonging to the 2 vessel classes were identified. The performance of the MPS was compared to the Vesselness thresholding (VT) by blindly grading on a 0-5 scale the accuracy of vascular tree depiction.

**Results:** The semiquantitative analysis clearly showed that MPS achieved greater accuracy in vessel display (scores 4-5 in 88% of the test-sample) than VT (scores 2-3 in 74% of the test-sample). In particular, false positives were the main pitfall of VT compared to MPS.

**Conclusion:** Combining the information obtained from Vesselness and R2* maps, the MPS substantially increased sensitivity and specificity of the monoparametric tresholding based on vesselness images only.

**Keywords:** brain veins, Vessel Enhancing Diffusion, R2* map, Expectation Maximization algorithm, multiparametric segmentation

**Podium presentation**