

State of the Art I: Why We Need a Multi-Modality Diagnostic Approach for CCSVI

Robert Zivadinov

¹Buffalo Neuroimaging Analysis Center, Department of Neurology, University at Buffalo, State University of New York, Buffalo, NY, USA

Abstract:

Background: The extra-cranial venous system is complex and not well studied in comparison to peripheral venous system. A newly proposed vascular condition, named chronic cerebrospinal venous insufficiency (CCSVI), described initially in patients with multiple sclerosis (MS) has triggered intense interest in better understanding of the role of extra-cranial venous anomalies and developmental variants.

Methods: So far, there is no established diagnostic imaging modality, non invasive or invasive, that can serve as “gold standard” for detection of these venous anomalies. However, consensus guidelines and standardized imaging protocols are emerging. Most likely, a multimodal imaging approach will ultimately be the most comprehensive means for screening, diagnostic and monitoring purposes. Further research is needed to determine the spectrum of extra-cranial venous pathology and to compare the imaging findings with pathological examinations.

Conclusions: The ability to define and reliably detect noninvasively these anomalies is an essential step toward establishing their incidence and prevalence. The role for these anomalies in causing significant hemodynamic consequences for the intra-cranial venous drainage in MS patients and other neurologic disorders, and in aging, remains unproven.

Ultrasound contrast imaging of brain hemodynamic and perfusion

Marcello Mancini, M.D.

Institute of Biostructure and Bioimage – CNR

Naples, Italy

Studies based on histopathological techniques and on MR imaging demonstrate hypoxia-like brain tissue injury or thrombosis of small veins in patients with Multiple Sclerosis (MS). Applying dynamic susceptibility contrast Magnetic Resonance Imaging, cerebral mean transit time values were found to be significantly prolonged in MS patients. Recent newly developed ultrasound techniques extend our ability to study the cerebral hemodynamics in patients with neurological disease beyond the conventional blood flow velocity analysis. Different ultrasound methods are currently under investigation that either qualitatively or quantitatively describe brain perfusion. The most widely used technique is bolus kinetics. After applying a ultrasound contrast agent bolus, time intensity curves of the wash-in and wash-out phase of the bolus passage through the brain are registered by imaging at a set frame rate and analyzing the ultrasound intensity in a given region of interest. Based on the time intensity curves, different parameters can be extracted such as peak intensity, time to peak, mean transit time, and incremental time. These parameters can be displayed in a tissue region of interest defined by the examiner. We present the application of contrast enhanced ultrasound (CEUS) to assess *global cerebral circulation time* (CCT) in patients with multiple sclerosis (MS). The method is based on the assumption that the time required by an ultrasound contrast agent to pass from the cerebral arteries to the veins should be prolonged in patients with vessel disorders. Our results suggest that a microvascular or venous outflow impairment could be associated with MS. The CEUS measurement of CCT may be useful tool to disclose cerebral microcirculatory dysfunction in MS patients.

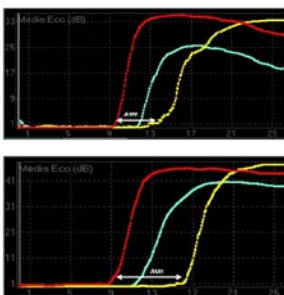
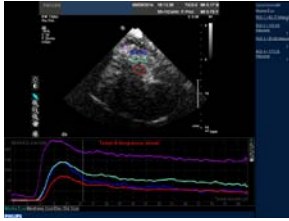


Fig. 1 The time-intensity curve analysis displays the acoustic intensity (in dB) during acquisition time in three different region of interest: the carotid artery, thyroid parenchyma without artery/vein, Internal Jugular Vein. The wash-in curves were analysed and three parameters were measured for the ROI: Arrival Time, Time To Peak and Absolute Intensity Peak.

Fig.2 The CCT in a MS patient (bottom) and in a control subject (top). The difference was evident (CCT_L in control subject was 3.3 s, in MS patient was 6.9s.. The red lined curve depicts the arterial signal, the green lined curve represents tissue signal and yellow lined curve represents the venous signal.

Ultrasound cerebral perfusion imaging is a technique of microvascular imaging that was introduced in the late 1990s. The main clinical focus has been on stroke patients. High MI phase inversion harmonic imaging of the diencephalic plane using the bolus administration of 2.5 mL SonoVue™ (Bracco Imaging) was applied using ultrasound instrument (Philips iU22), equipped with a phased-array transducer (2 MHz). After acquisition (36 to 40 frames), the radiofrequency data were transferred to a PC for further offline analysis. Off-line evaluation comprised region-wise analysis of time-intensity curves (TIC) of predefined ROIs and calculated time-to-peak intensity parameter images. US examinations were performed unilaterally with the transtemporal approach. Standard sonographic brain imaging starts in the axial plane with the probe positioned in the orbitomeatal line. The butterfly-shaped hypoechoic mesencephalic brainstem appears in the center of the image and serves as an orientation structure. Most brain structures exhibit a low echogenicity. The hypoechoic mesencephalic brainstem is surrounded by the hyperechoic basal cisterns. The hyperechoic aqueduct in the tectum is easily identified. A hyperechoic midline represents the 'brainstem raphe'. By tilting the probe upwards the diencephalic and ventricular plane can be displayed giving view to the third ventricle and the frontal horns of the lateral ventricles as anechoic zones bordered by hyperechoic lines where the ultrasound beam meets the ependyma in an orthogonal plane. The basal ganglia are not distinguishable from each other and the white matter because all exhibit a low echogenicity. Visualization of the M2 segment of the middle cerebral artery (MCA) after echo contrast agent injection ensured the correct position in the diencephalic plane. The field of view was set to an imaging depth of 10 cm; the sector angle was 90°. All examinations were performed with the left-sided temporal

approach and were digitally recorded and evaluated offline. Regional cerebral echo contrast enhancement was quantified using TIC. Peak intensities (PI), , and time to peak intensities (TPI)s, and bolus arrival time (AT), were calculated from a model function that was fitted to the measured curve in at least mean square sense. Quantitative data were calculated for the following manually placed ROIs: in the ipsilateral hemisphere, posterior parts of the thalamus, anterior parts of the thalamus, lentiform nucleus, white matter, and MCA (M2 segment) (see Figure 3).



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TBI and hemodynamic changes in the brain

James R. Stone, MD, PhD

One of the most serious health issues facing individuals under the age of 35 is traumatic brain injury (TBI). In the United States alone, it is estimated that 3.5 million individuals sustain a TBI each year, with 275,000 hospital admissions and 52,000 deaths as a result of this disease process. Cerebrovascular pathology is known to play a key role in the morbidity and mortality associated with TBI. Post-mortem evaluations of patients with TBI routinely demonstrate evidence of ischemia. Although the precise nature of TBI-induced ischemia is not entirely known, cerebral vasospasm, hyperemia, global edema, and uncoupling of cerebral blood flow and metabolism have all been observed in patients with this disease process. Also observed is disruption of the blood brain barrier, with concomitant loss of cerebral immune privilege, infiltration of peripheral leukocytes, expression of pro-inflammatory cytokines, and increased production of reactive oxygen species (ROS). The current presentation will review the hemodynamic changes and cerebrovascular pathology that are associated with TBI. These topics will be considered both globally and at the cellular and molecular level to provide insight into the range of cerebrovascular pathology seen in TBI, while examining common underlying mechanisms that may play a role in this disease process. Also considered will be TBI resulting from explosive devices and emerging evidence suggesting particular vulnerability of the cerebral vasculature to this injury mechanism.

Imaging of the Microvasculature

Saturday March 28 9:15 to 9:35

Session 1: Hemodynamics of the brain

Chairs: Dr. Marcello Mancini & Dr. Mark Haacke

E. Mark Haacke, PhD

Background: The brain's vasculature, as well as perfusion and blood flow, can be probed with and without contrast agents using MRI. Recent evidence shows that vessels as small as 100 μ to 250 μ can be seen with conventional clinically accessible MR angiographic methods in humans and as small as 40 μ in animals.

Objectives: To assess the current state-of-the-art MR imaging methods with and without contrast agents to study the microvasculature of the brain.

Methods: To investigate arterial and venous blood vessels without contrast agent, we review conventional MRA and susceptibility weighted imaging (SWI) methods as well as an interleaved multi-echo version of SWI that includes a short echo MRA. These time-of-flight (TOF) imaging methods have limited SNR and so alternate methods must be sought to improve vessel visualization further. To improve the vessel visibility, two types of contrast agent are evaluated: T1 reducing methods and iron particle T2* and susceptibility based methods such as susceptibility weighted imaging and mapping (SWIM). These are also used to study macromolecular exchange between the venous system and the cerebral spinal fluid (CSF).

Results: With no contrast agents, it is viable to collect 0.5mm isotropic resolution in a reasonable time period. With a T1 reducing agent, the best resolution to date is 0.25mm x 0.25mm x 0.5mm allowing vessels as small as 100 μ to 250 μ to be seen. With a T2* iron based contrast agent, in an animal model, the best resolution to date is 42 μ x 42 μ x 250 μ . Using iron tagged dextran it is possible to see the exchange of the dextran macromolecule across the vessel wall into the veins.

Conclusion: MRA and SWI offer two powerful means to study the neurovascular system.

Keywords: MR angiography, susceptibility weighted imaging, cerebral spinal fluid

Hugues Chabriat

Abstract

Imaging of Brain Microvascular Disorders: lessons from the CADASIL model.
Hugues Chabriat, MD PhD; Department of Neurology, GH Lariboisiere, APHP, INSERM UMRS1161, University Paris 7 Denis Diderot, Paris France.

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an archetypal ischemic small vessel disease responsible for stroke, dementia and severe disability. The disease is caused by different mutations of the NOTCH3 gene on chromosome 19. CADASIL is considered as a unique model for investigating the classical imaging markers of small vessel disease and for understanding their exact clinical correlates. Imaging studies were previously obtained for determining the natural history of subcortical ischemic lesions, evaluating the cortical consequences of incident lesions, measuring the development of cerebral microstructural and morphological changes. Imaging markers were also recently identified for prognostication and stratification in this model of small vessel disease. Finally, imaging data were found useful for better understanding the pathophysiology of white-matter lesions (so-called “leukoaraiosis”) parallel to studies obtained in the animal model of the disease. The results strongly support that different types of white-matter lesions are present in CADASIL that may be also detected in sporadic small vessel disease.

ISVNV Naples, Sa 28 March 2015, 10:30AM-10:50AM

Title: **2D and 3D analysis of vessels in the retina and the brain**

Speaker: Prof. Bart ter Haar Romeny, Ph.D.^{1,2}

¹Eindhoven University of Technology, Eindhoven, the Netherlands

²Northeastern University, Shenyang, China

Abstract:

Quantitative measurement of geometrical and physiological properties of blood vessels in the retina may indicate early stages of brain and systemic diseases in an efficient and cost-effective way. Retinal vasculature is brain vasculature, and can be imaged easily at high resolution with optical fundus or OCT cameras. Breakdown of the blood-brain barrier, as in diabetes, leads to marked vascular changes, which can be signaled early. This is e.g. exploited in large screening programs for diabetes worldwide.

We will discuss how typical quantitative imaging biomarkers are measured automatically, as curvature and tortuosity, width, arteriovenous ratio, bifurcation analysis, micro-bleeds, aneurysms and stenosis, angiogenesis, fractal dimension etc. For the enhancement, tracking and segmentation of the tiny vessels we exploit highly robust methods learned from modern insight in brain mechanisms of visual perception. Optical imaging techniques have revealed multi-scale and multi-orientation columns in the visual cortex, which we model mathematically. The micro-vascular analysis can be done in 2D (retina) and 3D (brain, heart).

Computer algorithms also enable quantitative analysis and smart interactive 3D visualization of functional imaging, such as 4D blood flow. Flow in larger vessels is still poorly understood. Modern graphics cards ('game cards') enable cheap and massively parallel renderings. We give examples of modern visualization techniques, inspired by brain connectivity visualization, of 3D/4D flow patterns in brain aneurysms, and aortic arch flow turbulence as an indicator for valve functioning.

The message of the presentation is that quantitative analysis of micro-vasculature, and interactive 4D visualization of complex flow parameters in larger vessels is now clinically feasible and accessible.

A NOVEL SONOGRAPHIC METHOD FOR REPRODUCIBLE JUGULAR VEIN PULSE WAVE ASSESSMENT

Paolo Zamboni, Francesco Sisini, Erica Menegatti, Giacomo Gadda, Mirko Tessari, Mauro Gambaccini

Vascular Diseases Center, University of Ferrara, Ferrara, Italy

Aims: We investigated in two phases respectively the feasibility to reliably and non invasively derive the jugular venous pulse (JVP) by means of Ultrasound (US) equipment, and to preliminarily compare JVP in normal people with patients affected by extracranial venous obstructive diseases, typical of the chronic cerebrospinal venous insufficiency (CCSVI).

Methods: Phase 1. Three young healthy subjects underwent B-mode US scan of the internal jugular vein (IJV) in order to acquire a sonograms sequence in the transversal plane.

On each acquired sonogram we manually traced the IJV contour and measured the cross sectional area (CSA) as well as perimeter. The CSA dataset represents the US-JVP.

The arterial distension wave-form of the subjects were compared with their US jugular diagram.

The correlation between the CSA with the perimeter was assessed during the cardiac cycle to verify the IJV distension. For each subject a short sonogram sequence of 4.8 seconds has been recorded.

We compared 390 manually traced profiles of the IJV cross sectional area with corresponding values automatically calculated by an algorithm made in house.

Phase 2. We blindly compared ten healthy controls with twenty CCSVI patients by the means of the above reported new diagnostic methodology, synchronized with the ECG trace.

Results: Phase 1. For all subjects the US-JVP showed a periodic behaviour. For the three subjects, the Fourier transform showed the pulse duration of the jugular vein. For all the subjects the CSA was found correlated with the perimeter (Pearson coefficient $R > 0.9$) indicating that the IJV in supine position is distended. For all the subjects the mean sensitivity, specificity and diagnostic accuracy resulted around 90%, by comparing the 390 manual tracing with the algorithm. This indicates that JVP can be reliably measured through a rapid analysis of the recording of a real time 5 seconds of sonograms sequence of the IJV.

Phase 2. The new methodology to assess the IJV functionality has been compared in a blind pilot study where the JVP was analyzed together the ECG. The analysis clearly shows typical and physiologic curves in the control group respect to abnormalities and high variability assessed in the CCSVI group.

Conclusions: We have shown that a diagram reflecting the JVP can be obtained by analysing an US B-mode movie. Both acquisition and post processing analysis by the means of the developed algorithm require a short time and reduce the operator dependency. Moreover, the significance of the JVP in the CCSVI screening seems promising and warrants a large, blinded, multicenter study.

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

Clive B Beggs¹, Simon J Shepherd¹, Pietro Cecconi² and Maria Marcella Lagana²

1. Medical Biophysics Laboratory, University of Bradford, Bradford, BD7 1DP, UK
2. Fondazione Don Carlo Gnocchi ONLUS, IRCCS S. Maria Nascente. Milan, Italy

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].

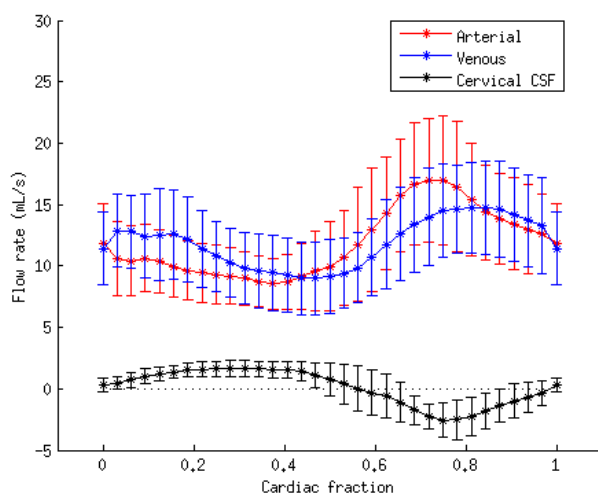


Figure 1. Aggregated fluid flow rates.

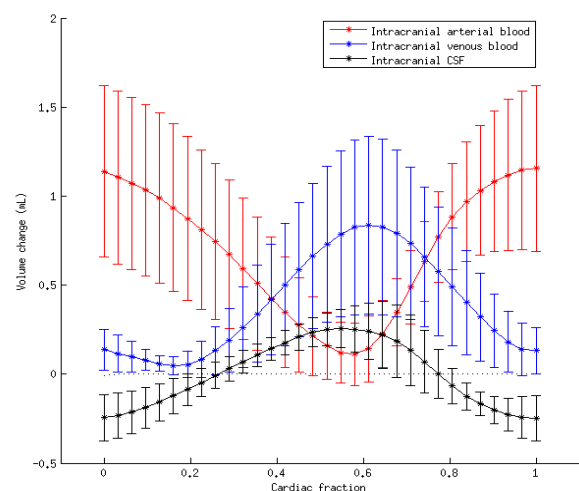


Figure 2. Relative intracranial fluid volumes.

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Update in computational fluid modelling of the brain

Mauro Ursino

Several aspects concur in making the cerebral circulation extremely complex: i) the presence of diffuse anatomical pathways among cerebral vessels (both in the intracranial arterial and extracranial venous circulations); ii) the presence of sophisticated mechanisms which regulate cerebral blood flow following pressure changes and changes in blood gas content; iii) the occurrence of a portion of this circulation within a closed space (the skull and neuroaxis) with a limited volume storage capacity. A deeper understanding of how these complex factors interact reciprocally, and of their possible role in pathological conditions, may be attained with the use of mathematical models and computer simulation techniques.

Aim of the presentation is to illustrate the complex mechanisms affecting the cerebral hemodynamics, by making use of computational models developed in past years, and showing some practical examples.

The first part of the presentation is focused on the intracranial circulation, laying emphasis on the role of cerebrovascular regulatory mechanisms. A few pathological cases are simulated, to illustrate the complexity of factors operating on brain hemodynamics. An example considers the case of patients with reduced storage capacity and altered CSF circulation (a condition, for instance, typically occurring in patients with severe head injury). In these cases, instability of intracranial dynamics may lead to uncontrollable increase in intracranial pressure, with the development of large ICP waves [1]. A further example simulates hemodynamics in patients with unilateral internal carotid artery stenosis; in this case, local blood flow regulation is progressively lost in the ipsilateral territory with the presence of a steal phenomenon, while the anterior communicating artery plays the major role to redistribute the available blood flow [2].

The second part presents a very recent extension of this model, in which a detailed description of the extracranial venous pathways (jugular veins, vertebral-azygos vein complex, collateral anastomoses) are included. The model accounts for the changes in jugular vessels lumen occurring when passing from supine to standing, and simulates how these changes can affect flows and pressures in specific points of the system [3]. Furthermore, the model provides quantitative predictions on how this redistribution can be altered by stenotic patterns, and how a failure of the extracranial venous drainage may be reflected in the upstream intracranial circulation.

We claim these models may have a great perspective value, to help clinicians in reaching a deeper understanding of the multiple mechanisms operating on the brain circulation, and to be acquainted on the complex effects of pathological alterations in brain vessels.

Key references

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Saturday 11:50AM-12:10PM –

Fluid Dynamic Influences on Cerebrovascular Endothelial Activation Responses

Emily V. Stevenson, J. Winny Yun, Seiichi Omura, Fumitaka Sato, Ikuo Tsunoda, Alireza Minagar, Felix Becker, Trevor Castor, Pierre-Olivier Couraud, Ignacio A. Romero, Babette Weksler, J Steven Alexander, LSUHSC-Shreveport Molecular and Cellular Physiology, Microbiology, Virology, Neurology, Shreveport, Louisiana, USA, Cochin Institute, Inserm, Weill Cornell Medical College, The Open University Walton Hall.

Alterations in blood flow and vascular shear stress are known to induce multiple changes in venous and arterial endothelial cells, including modifications in pro- and anti-inflammatory gene expression, cell differentiation and proliferation, tight junction maintenance, and overall vascular homeostasis. A role for vascular disturbances has also been increasingly apparent in the progression of multiple neurological disorders, such as Multiple Sclerosis and Alzheimer's disease, particularly in initiation and progression of inflammatory processes and potentially blood-brain barrier disturbances. Because changes in vascular shear stress have been implicated in the progression of atherosclerotic disease and in the progression of inflammatory process, we hypothesized that shear stress alterations would lead to inflammatory activation of cerebral endothelial cells. To test this, we exposed human brain endothelial cells (hCMEC-D3) to high or low levels of non-linear shear using microcarrier cultured brain endothelial cells to compare the effects on endothelial activation. We found amyloid precursor protein (APP) was basally expressed in hCMEC-D3 and was released into endothelial microparticles (EMPs) in response to high fluid shear. Similarly, the neurolymphatic marker, lymphatic vascular endothelial hyaluronic acid receptor LYVE-1 was increased in both cells and EMPs in response to high fluid shear. The shear dependent transcription factor Kruppel-like factor 4 KLF-4 was abundant in hCMEC-D3 and appears to increase in response to high and low shear treatment and was transferred into EMPs under both conditions. The tight junction protein Occludin was also increased in hCMEC-D3 in response to both levels of fluid shear, with cleaved forms apparent in sheared MPs. Importantly we found that caveolin-1 was shed into EMPs in response to shear, consistent with these structures as caveolae discharged by cells following exposure to shear. Supported by Aphios Corporation 'Alzheimer's Disease Therapeutic' (5R44AG034760) and the Feist Cardiovascular Institute (LSUHSC-S).

Saturday 4:00PM-4:20PM – In Endothelial function, the glymphatic system and New Drug Development

Endothelial dysfunction in neurodegenerative disease

J. Winny Yun, Emily Stevenson, Seiichi Omura, Fumitaka Sato, Ikuo Tsunoda, Alireza Minagar, Felix Becker, Trevor Castor, Adam Xiao, J. Steven Alexander, LSUHSC-Shreveport Molecular and Cellular Physiology, Microbiology, Virology, Neurology, Shreveport, Louisiana, USA.

Inflammatory cytokines appear to promote forms of vascular stress in several neurodegenerative diseases and may trigger endothelial disturbances which contribute to blood-brain barrier breakdown and intensification of disease. Using bEnd3 brain endothelial cell model, we found that in response to exposure to TNF- α (20 ng/ml) + Interferon- γ (1000 U/ml) (‘T/I’) bEnd3 endothelial cells released microparticles from both apical and basolateral domains, (AMPs and BMPs respectively.) Lymphatic vascular endothelial hyaluronic acid receptor (LYVE-1), Prospero homeobox 1 (Prox-1) and vascular endothelial growth factor receptor (VEGFR-3)/Flt-4 have been previously described as ‘neurolymphatic’ biomarkers found in tissue and serum samples in RR Multiple Sclerosis and SP Multiple Sclerosis. These biomarkers, as well as amyloid precursor protein (APP) were also found to be expressed by bEnd3 brain endothelial cells, and were transferred into bEnd3 derived AMPs following T/I-stimulation. The vascular association of these biomarkers in the CNS in distinct clinical forms of MS and experimental neurovascular forms of stress now indicates an endothelial origin for these markers. Interestingly, T/I stimulation also potently induced the transfer of caveolin-1, an important caveolar constituent from bEnd3 brain endothelial cells into AMPs. Similarly, T/I stimulated bEnd3 cells to also release membrane cholesterol, (measured as BODIPY-cholesterol fluorescence) another important caveolar component, consistent with endothelial microparticles as fluid phase caveolae liberated by cytokine-activated endothelium. By comparison, endothelial nitric oxide synthase (eNOS) was detected within endothelial cells and was decreased by T/I treatment; eNOS also appears to be transferred to AMPs consistent with these particles potentially representing a shed form of circulating eNOS. These findings suggest that neurolymphatic markers induction observed in forms of MS and other of neurodegenerative diseases may represent partitioning of these biomarkers within caveolae which may segregate signaling modules related to neurovascular disease. Supported by Aphios Corporation ‘Alzheimer’s Disease Therapeutic’ (5R44AG034760) and the Feist Cardiovascular Institute (LSUHSC-S).

“Venous abnormalities in Meniere Disease”

P.M.Bavera; P. Cecconi; D. Alpini; F. Di Bernardino

The presentation will be of approximately 15/20 slides, including title and conclusions in respect of the assigned timetable.

A brief definition of the Meniere Disease, with principal symptoms

Correlations between these symptoms and those usually present in CCSVI affected Patients (mainly Multiple Sclerosis Patients)

Most evident and frequent results in Meniere Disease compared with those with over 2000 CCSVI MS Duplex exams.

Anatomic differences and localizations between the two groups of patients at Duplex exams.

MRI imaging of MS Patients and Meniere Disease Patients, with comparison and/or differences (anatomical, morphological)

Conclusions that mainly highlight the characteristics of the venous abnormalities within Meniere Disease.

Advances in Idiopathic Intracranial Hypertension Pathogenesis: a Focus on Sinus Venous Stenosis

Roberto De Simone, Angelo Ranieri

Headache Centre

Dpt. of Neurosciences, Reproductive Sciences and Odontostomatology
University of Naples "Federico II"

Idiopathic Intracranial Hypertension (IIH) is an enigmatic condition characterized by a near daily headache, papilledema, transient visual obscurations, diplopia, vertigo and tinnitus, almost always encountered in overweight women of childbearing age. Symptoms arise from an hypertensive intracranial status which is not associated with any detectable cause.

IIH may run without papilledema (IIHWOP) in a part of the patients. IIHWOP may be indistinguishable on clinical basis from primary chronic headache. Available literature evidences suggest that IIHWOP could represent a possible, largely underestimated, risk factor for migraine progression.[1]

To date, the presence of sinus venous stenosis at Magnetic Resonance Venography is considered a reliable radiologic marker of IIH.[2] Sinus stenosis is considered secondary to the raised cerebrospinal fluid (CSF) pressure as it may resolve after CSF withdrawal. However, in recent years the efficacy of endovascular venous stenting in IIH treatment has been consistently reported,[3] strongly suggesting that sinus stenosis should be viewed as a causative factor rather than a secondary phenomenon.

We propose that in subjects carrying one or more collapsible segments of large cerebral venous collectors, exposed to a number of different promoting factors, sinus venous compression and CSF hypertension may influence each other in a circular way, leading to a new relatively stable venous/CSF pressures balance state at higher values. The mechanism relay on self-limiting venous collapse (SVC) feedback-loop between CSF pressure, that compresses the sinus, and the consequent venous pressure rise, that in turn increases CSF pressure. The result is the "coupled" increase of both pressure values, a phenomenon not expected in presence of sufficiently rigid central veins. Once the maximum stretch of venous wall is reached the loop stabilize at higher venous/CSF pressure values and become self-sustaining, therefore persisting even after the ceasing of the promoting factor. Notably, the SVC is reversible provided an adequate perturbation is carried to whichever side of the loop such as sinus venous stenting, on one hand, and CSF diversion or even a single CSF withdrawal by lumbar puncture (LP), on the other. The SVC model predicts that any condition leading to an increase of either, cerebral venous or CSF pressure may trigger the feedback loop in predisposed individuals.

If the SVC might be regarded as a crucial IIH predisposing mechanism, a primary event triggering the CSF and sinus venous higher pressure balances shift is probably always required.

Migraine with and without aura, a disease sharing with IIH a much higher prevalence among women of childbearing age, is associated with waves of significant brain hyperperfusion. These may lead to the congestion of large cerebral venous collectors and could represent a common SVC promoting condition in susceptible individuals and this could account for the high frequency of IIHWOP observed in headache sufferers.

The SVC model give reason of the high specificity and sensitivity of sinus stenosis as IIH predictor and of the multiplicity of the factors that have been found associated with IIH. Finally, the SVC model fully explain the enigmatic longstanding remissions that can be commonly observed after a single LP with CSF subtraction in IIH with or without papilledema.

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Advances in Treatment Strategies of Extracranial Venous Disease

Hector Ferral, MD
Senior Clinical Educator
NorthShore University HealthSystem
Evanston, IL.

Abstract

Dr. Paolo Zamboni was the first investigator to report the management of internal jugular vein and azygos vein stenotic lesions to improve symptoms in patients with multiple sclerosis (1). His original report describes angioplasty of the stenotic lesions using 8 mm and 10 mm angioplasty balloons (1). Dr. Zamboni called this entity the “Chronic Cerebrospinal Venous Insufficiency” or CCSVI (1).

The endovascular management of CCSVI is controversial. The work of some investigators has supported Zamboni’s original contribution(2-6), however, other investigators have not confirmed the encouraging results reported by Zamboni (7) and for this reason, the concept of CCSVI and its management has been strongly criticized (8, 9).

Endovascular management of jugular vein and azygos vein stenotic lesions has mainly focused on the use of balloon angioplasty (2, 3, 10) and certain modifications to the angioplasty technique, including the use of double balloons and cutting balloons have been employed. Measurement of the target vein is imperative; Vein measurement using conventional venography with multiple projections (2, 3) and Intravascular Ultrasound (IVUS) are the most important methods employed for precise vein measurement (4, 7, 11). Endovascular stents have also been used to treat jugular and azygos vein stenoses (6), however, reports of complications with the use of endovascular stents have decreased the enthusiasm for their use in these cases (12).

The current presentation will focus on the technical advances in performing endovascular management of CCSVI. Vein measurement and therapeutic methods will be discussed along with the potential advantages and disadvantages.

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Venous dysfunction and neurodegenerative diseases

Chih-Ping Chung MD PhD

Taipei Veterans General Hospital, National Yang Ming University, Taipei, Taiwan

Several neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, normal pressure hydrocephalus, etc. have been reported associated with cerebral or/and extracranial venous abnormalities. The present lecture will focus on the current evidences linking venous abnormalities with AD and cerebral small vessel disease in the elderly, e.g. age-related white matter changes. Meanwhile, the relationship between jugular venous reflux (JVR) and multiple neuropsychological performances in patients of AD, results of our latest study, will be presented. At last, a discussion about the postulated mechanisms how venous drainage impairment lead to dysfunctions in AD will be provided.

Clinical Applications of Venous Treatment

Recent data from the literature suggest a greater role of chronic venous insufficiency in the pathogenesis of a variety of brain disorders. The goal of this talk is to review the contributions made in 2014 to our enhanced understanding of the safety and efficacy of the endovascular or open surgical treatment of chronic venous obstruction in patients with a variety of pathologies including multiple sclerosis, transient global amnesia, Alzheimer's disease, Parkinson's disease, postural orthostatic tachycardia syndrome, transient monocular blindness, headaches, and spontaneous intracranial hypertension. Open surgical interventions including, but not limited to operative venous bypass, transposition, venoplasty, and vein interposition have been reported. Endovascular procedures detailed in the medical literature include balloon angioplasty, cutting or scoring balloon angioplasty, self-expanding and balloon expandable stent placement, and stent-grafting. In general, all these therapies have been used to treat stenosis and/or occlusions of the jugular and/or azygous veins associated with increased collateral venous drainage. The relationship between anatomic findings and any symptoms related to the range of neurological disorders listed above has not been established and further research is required.

MICHAEL D. DAKE, M.D.

Thelma and Henry Doelger Professor (III)

Department of Cardiothoracic Surgery
Stanford University School of Medicine
Falk Cardiovascular Research Center

300 Pasteur Drive

Stanford, CA 94305-5407

t: [650.725.6407](tel:650.725.6407)

f: [650.725.3846](tel:650.725.3846)

e: mddake@stanford.edu

Is there a role for mast cells dependent synthesis of Endothelin-1 in neurodegenerative diseases?

Pedro D'Orléans-Juste⁻¹, Louisane Desbiens, Denis Gris⁻²

Departments of Pharmacology⁻¹ and of Pediatrics⁻², Faculty of Medicine, Université de Sherbrooke, Sherbrooke, PQ, Canada

Abstract:

Background: In the central nervous system mast cells are found in proximity of neurons and blood vessels. During inflammation, activated mastocytes releases several proteases among which chymase is known to generate the potent vasoactive peptide, Endothelin-1 (ET-1). It is of interest that both mast cell density and ET-1 levels are significantly increased in neurological disorders such as Multiple Sclerosis.

Principal Aim: To identify the contribution of chymase and ET-1 in a murine model of experimental allergic encephalomyelitis (EAE).

Methods: The ET-1 producing capacity of a mouse chymase isoform Mast Cell Protease 4 (mMCP-4) will be compared to that of its human isoform using a combined recombinant/triple tof mass spectrometry approach. In addition, the contribution of systemic mMCP-4 in radiotelemetry instrumented-conscious mice will be assessed. Finally, clinical scores (from 0, normal mouse to 5, moribund state) will be assessed in WT or mMCP-4 KO mice with induced EAE.

Results and Conclusions: The present study demonstrates that both mouse and human chymases are involved in the synthesis of ET-1. Furthermore, preliminary results show reduced morbidity of EAE-induced mice genetically repressed for mMCP-4. We conclude that among several proteases secreted by mast cells in the vicinity of spinal lesions, chymase may play a significant role in the morbid events occurring in the mouse model of Multiple Sclerosis.

Endothelin- 1 as a potential target for chronic brain hypoperfusion

Jacques De Keyser, MD, PhD, Free University of Brussels (VUB), Department of Neurology, Brussels, Belgium

In the brain endothelin-1 (ET-1) is produced and released by endothelial cells lining the blood vessels and by astrocytes. ET-1 exerts its actions through two G-protein coupled receptors subtypes known as ETA and ETB receptors. In basal conditions, the expression of ET-1 in the brain is low, with concentrations of ET-1 in the picomolar range and hardly detectable by immunohistochemical techniques. Significant expression and release of ET-1 by reactive astrocytes occurs in acute CNS injuries, such as ischemic stroke and subarachnoid hemorrhage. It also occurs in a number of neurodegenerative disorders, including Alzheimer's disease, multiple sclerosis (MS), and subcortical vascular dementia (Binswanger's disease), which are all associated with chronic brain hypoperfusion. In patients with MS we have been able to show a relationship between chronic brain hypoperfusion and increased ET-1 levels. We found that, compared to controls, plasma ET-1 levels in MS subjects were significantly elevated in blood drawn from both the internal jugular vein and a peripheral vein. The jugular vein/peripheral vein ratio was 1.4 in MS subjects versus 1.1 in controls, indicating that in MS, ET-1 is released from brain to the cerebral circulation. ET-1 immunohistochemistry on postmortem white matter brain samples suggested that the likely source of ET-1 release were reactive astrocytes in MS plaques. Using arterial spin labeling MRI to noninvasively measure CBF we assessed the effect of the administration of the ET-1A/B receptor antagonist bosentan. CBF was significantly lower in MS subjects than in controls, and increased to control values after bosentan.

Chronic brain hypoperfusion in animal models induces mitochondrial energy failure and oxidative stress. White matter is more susceptible than gray matter, and shows axonal degeneration, apoptosis of oligodendrocytes, myelin breakdown, inflammatory reactions and gliosis. However, chronic cerebral hypoperfusion in rats is also associated with cognitive impairment, and neuronal loss in the hippocampal CA1 region. Axonal degeneration, apoptosis of oligodendrocytes, myelin loss and hippocampal atrophy have been observed in MS, subcortical vascular dementia and Alzheimer's disease. Our finding that reduced CBF in subjects with MS is reversible with an ET-1 antagonist opens the door for exploring new therapeutic approaches for neurodegenerative disorders associated with chronic brain hypoperfusion. ET-1 antagonists are available and are a possible strategy. Another approach consists in targeting the mechanisms leading to enhanced ET-1 expression in reactive astrocytes. In MS there is evidence that ET-1 upregulation in reactive astrocytes may be caused by cytokines that are elevated in MS plaques, including tumor necrosis factor- α and interleukin-1 β . Targeting these inflammatory pathways might reduce ET-1 expression, restore brain perfusion and slow down disease progression. The underlying mechanisms with regard to Alzheimer's disease and subcortical vascular dementia may be similar, although other mechanisms may be involved.

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Structural Changes in Extra-CNS Blood Vessels in Neurodegeneration

Marie-Luce Bochaton-Piallat, PhD

Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Venous abnormalities have been associated with different neurological conditions and the presence of a vascular involvement in multiple sclerosis (MS) has long been anticipated. In view of the recent debate regarding the existence of cerebral venous outflow impairment in MS due to abnormalities of the azygos or internal jugular veins (IJVs; *Zamboni et al., J Neurol Neurosurg Psychiatry, 2009; 80:392-399*), we have studied the morphological and biological features of IJVs in MS patients (*Coen et al., Cardiovasc Pathol, 2013, 22:33-38*).

We had the opportunity to investigate the histological features of vein specimens (provided by the Vascular Diseases Center and the Operative Unit of Vascular and Endovascular Surgery, S. Anna University-Hospital, Ferrara, Italy and by the Division of Clinical Pathology, Geneva University Hospitals, Geneva, Switzerland). We examined: 1) IJVs specimens from MS patients who underwent surgical reconstruction of the IJV and specimens of the great saphenous vein used for surgical reconstruction; 2) different vein specimens from a MS patient dead of an unrelated cause; and 3) autoptical and surgical IJV specimens from patients without MS. Collagen deposition was assessed by means of Sirius red staining followed by polarized light examination. The expression of collagen type I and III, cytoskeletal proteins (α -smooth muscle actin and smooth muscle myosin heavy chains), inflammatory markers (CD3 and CD68) were investigated.

Our results showed that the extracranial veins of MS patients exhibited focal thickenings of the wall characterized by a prevailing yellow-green birefringence (corresponding to thin, loosely packed collagen fibers) correlated to a higher expression of type III collagen. No differences in cytoskeletal protein and inflammatory marker expression were observed.

The IJVs of MS patients presenting a focal thickening of the vein wall are characterized by the prevalence of loosely packed type III collagen fibers, i.e. an altered collagen type I/III ratio, in the adventitia; this ratio is similar to that observed in fibrotic lesions but without the presence of myofibroblasts. The absence of inflammatory cells within the vein wall lesions suggests that the altered collagen I/III ratio is not secondary to an inflammatory disorder.

Our results establish for the first time a morphological and biological description of extracranial vein alteration in MS. These findings could account for the flow abnormalities occasionally described in MS. Further studies are required to determine whether the observed venous alterations play a role in MS pathogenesis.