6th International CSF Dynamics Symposium

Harn Museum of Art, 3259 Hull Road, Gainesville, Florida
June 16 & 17, 2022

Organized by Malisa Sarntinoranont & Marianne Schmid Daners

WELCOME TO THE CSF SYMPOSIUM

On behalf of the Bobby Jones Chiari & Syringomyelia Foundation and the organizing team, we welcome you to the 6th International CSF Dynamics Symposium in Gainesville, Florida. This year we have a diverse group of researchers with expertise in all aspects of CSF dynamics. Our aim is to provide a stimulating symposium that will showcase excellent researchers, increase collaboration between members of the group, and to help raise the field of CSF dynamics to greater notoriety.

Thank you for making the effort to be here and for making this symposium a success!

Malisa Sarntinoranont and Marianne Schmid Daners

SPONSORSHIP

The 6th CSF Dynamics Symposium is sponsored by the Bobby Jones Chiari & Syringomyelia Foundation and the Monkton Institute. The Monkton Institute, Inc., founded in 2002, is a private foundation that funds research and educational initiatives to better understand, diagnose and treat Arnold-Chiari malformation and associated problems of the brain stem. The Bobby Jones Chiari & Syringomyelia Foundation's mission is to advance knowledge through research and to educate the medical, allied sciences, and lay community about Chiari malformation, syringomyelia and related disorders. Please visit their website at **www.bobbyjonescsf.org**.

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The 6th CSF Dynamics Symposium is hosted by the University of Florida which has provided logistical and technical support.

PLENARY LECTURE, THURSDAY, JUNE 16TH, 9:15 – 10:15

ILLUMINATING THE CHOROID PLEXUS-CEREBROSPINAL FLUID SYSTEM

Maria K. Lehtinen

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Abstract. The choroid plexus (ChP) is a vital tissue located in each ventricle in the brain. The ChP is composed of two parallel sheets of epithelial cells with an intervening network of primarily non-neural cell types and vasculature. The ChP (1) produces cerebrospinal fluid (CSF) containing growth-promoting factors for the brain, (2) forms a blood-CSF barrier that gates communication between the central nervous system (CNS) and the systemic milieu, and (3) is implicated in CSF clearance functions (e.g., removal of toxic proteins including amyloid-beta). While ideally positioned to regulate brain function broadly, compared to other neural and non-neural brain systems, the ChP network is surprisingly poorly understood. Progress in understanding its role(s) has been hindered in large part by the lack of available tools for selectively accessing and controlling the ChP *in vivo*. In collaborations with others (Aviv Regev, Mark Andermann, Chris Moore, Jason Sutin, Ivy Lin, Benjamin Warf), we have adapted newly available tools to better understand ChP and CSF biology. We generated a cellular atlas of the ChP, elucidating its cell types and ventricle-specific identities throughout the mouse lifespan. In parallel, we adapted multi-photon imaging technologies that reveal *in vivo* activities and behaviors of ChP cells. We miniaturized a constant rate infusion test to determine intracranial compliance (C_i) and CSF resistance (R_{CSF}), providing insight to CSF dynamics (using Marmarou's model). Collectively, these approaches have uncovered a new mechanism by which the ChP contributes to CSF clearance during postnatal mouse development. We found that CSF K^+, accompanied by water, can be cleared through the ChP during mouse early postnatal development. ChP-NKCC1 augmentation results in increased CSF K+ clearance, increased cerebral compliance, and reduced circulating CSF in the brain without changes in intracranial pressure in mice. Moreover, ChP-specific NKCC1 overexpression in hydrocephalus mouse models mitigates ventriculomegaly. Collectively, our results implicate NKCC1 in regulating CSF K^+ clearance through the ChP during early postnatal development in mice. Collectively, our data highlight a role for the ChP in rapid compensation for alterations in CSF homeostasis under certain conditions and demonstrate the utility of targeted gene therapy to mitigate intracranial fluid accumulation.

1. Shipley, FB*, Dani, N*, Xu, H, Deister, C, Cui, J, Head, JP, Sadegh, C, Fame, RM, Shannon, ML, Flores, VI, Kishkovich, T, Jang, E, Klein, EM, Goldey, G, He, K, Zhang, Y, Holtzman, MJ, Kirchhausen, T, Wyart, C, Moore, CI, Andermann, ML#, Lehtinen, MK# (*, #, equal contribution). Tracking calcium dynamics and immune surveillance at the choroid plexus blood-cerebrospinal fluid interface. Neuron 2020 Nov. 25; 108: 623-639.

2. Dani, N*, Herbst, RH*, McCabe, C, Green, G, Kaiser, K, Head, J, Cui, J, Shipley, FB, Jang, A, Dionne, D, Nguyen, L, Rodman, C, Riesenfeld, SJ, Prochazk, J, Prochazkova, M, Sedlacek, R, Zhang, F, Bryja, V, Rozenblatt-Rosen, O, Habib, N#, Regev, A#, Lehtinen, MK# (co-senior authors). A cellular and spatial map of the choroid plexus across brain ventricles and ages. Cell 2021 May 27 184(11)3056-3074.

3. Xu, H*, Fame, RM*, Sadegh, C, Sutin, J, Naranjo, C, Syau, D, Cui, J, Shipley, FB, Vernon, A, Gao, F, Zhang, F, Holtzman, MJ, Heiman, M, Warf, BC, Lin, P-Y, Lehtinen, MK (*, equal contribution). Choroid plexus-NKCC1 mediates cerebrospinal fluid clearance during mouse early postnatal development. Nature Communications 2021 Jan. 19; 12:447

About the Presenter: Maria Lehtinen is Associate Professor of Pathology at Harvard Medical School at Boston Children's Hospital. Her research focuses on the mechanisms by which the choroid plexus - cerebrospinal fluid (CSF) system contributes to brain development and lifelong brain health. Dr. Lehtinen received her Ph.D. in Neurobiology from Harvard University where she trained with Dr. Azad Bonni on molecular mechanisms regulating neuronal survival and death. She carried out postdoctoral training first with Anna-Elina Lehesjoki's lab at the University of Helsinki, and then with Christopher A. Walsh at Harvard. Dr. Lehtinen established her own laboratory at Boston Children's Hospital in 2012, where she takes an interdisciplinary approach to study choroid plexus-CSF-based signaling in the brain, with applications ranging from neural development to age-associated neurologic diseases. Dr. Lehtinen currently holds the Hannah C. Kinney, MD, Chair in Pediatric Pathology Research and is a New York Stem Cell Foundation – Robertson Neuroscience Investigator.

Maria Lehtinen

~~**SESSION A, THURSDAY, JUNE 16TH, 10:15 – 10:40**~~ **(unable to attend)**

PLAUSIBILITY OF CHOROIDAL CSF PRODUCTION BY STANDING OSMOTIC GRADIENTS

Pooya Razzaghi[1], Eva K. Oernbo[2], Thomas Zeuthen[2], Nanna MacAulay[2], Vartan Kurtcuoglu[1]

[1] Institute of Physiology, University of Zurich, Zurich, Switzerland

[2] Department of Neuroscience, University of Copenhagen, Copenhagen, Denmark

Abstract. While it is generally accepted that CSF is produced primarily by the choroid plexus (ChP), the underlying mechanisms are still debated. With the ChP luminal surface extending into microvilli, the inter-microvillar spaces might form pools protected from intraventricular fluid motion, where solutes transferred from the epithelium may accumulate. This might create local osmotic gradients favoring trans-epithelial fluid movement into the ventricle according to the standing osmotic gradient (SOG) hypothesis. To determine whether OSGs could account for CSF production in the absence of other mechanisms, we created a mathematical model of solute-linked water transport in the ChP inter-microvillar space based on a simplified representation. The derivation thereof is shown in Fig. 1: Microvilli and the inter-microvillar spaces, where SOG might exist (b), are geometrically approximated (c). The blue region shows one inter-microvillar space. Panel (d) shows the same space with interfaces to the four adjacent microvilli and to the base of the luminal membrane of the epithelial cell. The green arrows indicate solute flux produced by transport mechanisms on the luminal membrane. Pooling of solutes in the inter-microvillar space might yield osmotic forces that draw fluid from the ChP epithelium. Panel (e) shows a circular cylindrical channel hydrodynamically equivalent to the inter-microvillar space shown in (d). A one-dimensional SOG model was derived from this equivalent geometry.

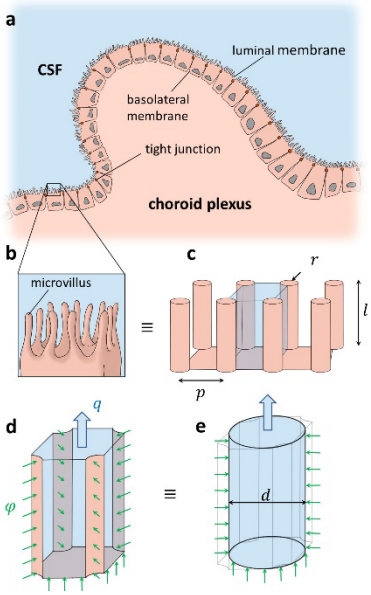


Fig. 1. Model domain derivation.

For model parameterization, we relied on rat data from [1]. Fluid velocity and solute concentration distribution along a simplified inter-microvascular space were determined through the following set of coupled steady-state differential equations originally proposed in [2]:

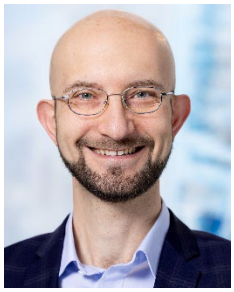
$$\frac{4\varphi(x)}{\rho \cdot d} + D\frac{d^2C}{dx^2} - C(x)\frac{dv}{dx} - v(x)\frac{dC}{dx} = 0 \qquad \frac{dv}{dx} = \frac{4L_p}{d}[C(x) - C_0]$$

φ: solute flux, x: distance, ρ: fluid density, d: diameter, D: diffusion coefficient, C: solute concentration, v: fluid velocity, Lp: permeability, C_0: bulk solute concentration

The model results predict that in the absence of other mechanisms, inter-microvillar SOGs may account for <0.1% of the expected CSF production rate (0.004 µl/min of 6.8 µl/min, [1]). We conclude that mechanisms other than standing osmotic gradients are likely responsible for most of the CSF production.

1. Oernbo EM et al. (2021). Cerebrospinal fluid formation is controlled by membrane transporters to modulate intracranial pressure. bioRxiv, https://doi.org/10.1101/2021.12.10.472067.

2. Diamond, JM, Bossert, WH (1967). Standing-gradient osmotic flow a mechanism for coupling of water and solute transport in epithelia. Journal of General Physiology 50, 2061-2083. (1967).



Vartan Kurtcuoglu

About the Presenter: Vartan Kurtcuoglu is an Associate Professor of Computational and Experimental Physiology at the Institute of Physiology of the University of Zurich, Switzerland. He is the current chairman and a founding member of the International Cerebrospinal Fluid Dynamics Society. His main research interests are fluid flow and associated transport processes in the mammalian body, with special focus on the central nervous system. The latter originated in his doctoral work on the computational modeling of fluid dynamics in the cerebral ventricular cerebrospinal fluid system. The goal of his laboratory is the integration of engineering, biological and medical research to address clinical needs.

QUANTIFICATION OF CARDIAC-RELATED NEURAL TISSUE MOTION IN TYPE 1 CHIARI MALFORMATION: A CASE CONTROL STUDY PRE- AND POST-SPINAL DECOMPRESSION SURGERY

Gwendolyn Williams[1], Dipankar Biswas[1], Michael Meggyesy[1], Audrey Fu[2], Ari Blitz[3], John Tew[4], John Oshinski[5], Francis Loth[6], Nathan Schiele[7], Bryn Martin[8], Mark Luciano[1]

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[2]Department of Statistical Science, University of Idaho, Moscow, ID, 83844, USA
[3]Department of Radiology, School of Medicine, Case Western Reserve University, Cleveland, OH, 44106, USA
[4]Department of Neurosurgery, University of Cincinnati Neuroscience Institute and University of Cincinnati College of Medicine, and Mayfield Clinic, OH, 45209, USA
[5]Department of Radiology & Imaging Science and Biomedical Engineering, Emory University, Atlanta, GA, 30322, USA
[6]Department of Mechanical and Industrial Engineering and Department of Bioengineering, Northeastern University, Boston, MA, 02115, USA
[7]Department of Chemical & Biological Engineering, University of Idaho, Moscow, ID, 83844, USA
[8]Alycone Therapeutics, Inc., Lowell, MA, 01852, USA

Abstract. Pathophysiology of Type I Chiari malformation (CMI) is not well understood but known to be a cerebrospinal fluid (CSF) related disorder. As CSF circulates with the cardiac cycle, pressure gradients between the CSF and cerebral blood flow (CBF) induce central nervous system (CNS) tissue motion which can result in tissue stretching and compression. We hypothesized that CNS tissue motion measurements would be abnormal in CMI patients and normalize after posterior fossa decompressive surgery.

Tissue motion in the rostral-caudal direction in three regions of interest (ROI) were quantified with two-dimensional phase-contrast magnetic resonance imaging (2D PC-MRI) in nine CMI patients, before and after surgery, and compared with those in 10 healthy volunteers. Displacement was quantified by integration of pixel velocity using the trapezoidal rule. Regions of interest were the upper spinal cord, the pontomedullary junction, and the cerebellar tonsil. Peak-to-peak regional displacement was quantified as the amplitude of displacement for any one ROI over the cardiac cycle. Peak-to-peak differential displacement was quantified as the displacement of either the cerebellar tonsil or the pontomedullary junction relative to the upper spinal cord. A linear mixed effects model determined significance at the 0.05 level.

We found significant differences ($p < 0.05$) between Chiari patients and controls in peak-to-peak regional displacement of the upper spinal cord (CMI: 0.51 ± 0.2 mm, Control: 0.72 ± 0.29 mm) and tonsil (CMI: 0.25 ± 0.15 mm, Control: 0.14 ± 0.05 mm), but not within the pons (CMI: 0.17 ± 0.07 mm, Control: 0.19 ± 0.03 mm). We also found significant differences ($p < 0.05$) in spinal cord to tonsil differential displacements between healthy controls and pre-operative CMI patients (0.30 ± 0.16, and 0.60 ± 0.29 mm, respectively). We did not see significant differences in regional displacement nor differential displacement between CMI patients pre- and post-operatively. These results show cardiac-induced neural tissue motion in the rostral-caudal direction is altered in the CMI disease state compared to healthy controls however, this tissue motion was not normalized after surgery.

Gwendolyn L.M. Williams

About the Presenter: Gwendolyn is currently a research specialist at Johns Hopkins School of Medicine in the Department of Neurosurgery working under Dr. Mark Luciano researching CSF related disorders. She acquired her bachelors of science in bioengineering from Oregon State University followed by her masters of science in biological engineering from University of Idaho with Dr. Bryn Martin as her masters advisor. Her research interests are focused on diagnostics and neuroimaging utilizing finite element analysis.

SESSION A, THURSDAY, JUNE 16TH, 10:40 – 11:05

FLOW-DEPENDENCE TO SHUNT OBSTRUCTION

Dr. Carolyn A, Harris[1], Prashant Hariharan[1], Christopher Roberts[2]

[1] Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI, 48202, USA
[2] Department of Biomedical Engineering, Wayne State University, Detroit, MI, 48202, USA

Abstract. Obstruction of flow through the ventricular catheter (VC) by tissue is one of the major causes of failure in ventricular shunt systems used to treat patients with hydrocephalus, particularly in the pediatric age group. Shunt failure has been attributed to many causes related to the dynamic nature of the ventricles. Flow distribution through the holes of the proximal catheter has previously been implicated as playing a role in driving obstruction. Building on the work of Galarza, Lin, and others, we have hypothesized that there is a relationship between the rate of flow through the holes of the catheter and the subsequent degree of obstruction of the hole. We use computational fluid dynamics to test this hypothesis and explore the relationship between physiological flow rate, shear, and pressure with respect to patient-specific ventricular size. Our model incorporates macroscale cerebrospinal fluid flow simulated using a reconstructed choroid plexus modeled from human tissue. We compare flow patterns through the holes of VCs inserted via frontal and posterior approaches, with the degree of obstruction in failed VCs from a previously established multi-center biobank. Quantitatively establishing relationships between the degree of VC obstruction, rate of flow through the VC holes, and the catheter location will help us understand whether specific strategies of catheter placement can be used to avert obstruction of the VC by tissue.

Carolyn A. Harris

About the Presenter: Dr. Harris is an Associate Professor of Chemical Engineering and Materials Science at Wayne State University with a joint appointment in Biomedical Engineering. Dr. Harris received her B.S. from Purdue University in 2006 and her Ph.D. from the University of Utah in 2011, both in Biomedical Engineering. She then pursued her postdoctoral research at the Seattle Children's Research Institute in 2014. Dr. Harris is nationally and internationally recognized as an expert in hydrocephalus due to her comprehension of the pathophysiology and her investigation into shunt obstruction and shunt infection utilizing unique in vitro model systems. In addition to her academic activities, Dr. Harris is deeply committed to improving public education and cultivating sincere connections between researchers and patients.

SESSION B, THURSDAY, JUNE 16TH, 11:35 – 12:00

MR-BASED MODELS THAT COUPLE STRESS AND FLOW WITHIN GLIOMA AND STUDIES OF BRAIN CLEARANCE VIA PERIVASCULAR NETWORKS

Julian A. Rey[1], James Ewing[2], Magdoom Kulam[1], Thomas H. Mareci[3], **Malisa Sarntinoranont[1]**

[1] Department of Mechanical & Aerospace Engineering, University of Florida, Gainesville, FL, USA
[2] Department of Neurology, Henry Ford Hospital System, Detroit, MI, USA
[3] Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, FL, USA

Abstract. Numerous *in vitro* experiments have shown that mechanical cues affect a glioma cell's phenotype, including its proclivity to infiltrate. These studies suggest that gliomas are sensitive to both structural stress and interstitial flow, and emphasize the need to characterize these properties for gliomas *in vivo*. We have developed 3D computational models of tumors embedded in the brain from dynamic contrast-enhanced MRI data. These subject-specific models account for underlying tissue structures, tumor growth, and vascular conditions *in vivo*, including heterogeneous vessel leakiness in the tumor that results in abnormal interstitial flow. We also consider the relative softness of glioma and brain tissue to produce new stiffness-sensitive predictions of stress in the tumor and surrounding host. Elevated interstitial fluid pressure produced tensile stress within the tumor that opposed the compressive stress produced by tumor growth[1]. This tensile effect was more pronounced in softer tissue and acted synergistically with tumor growth to elevate stress at the tumor rim. Use of a realistic geometry introduced heterogeneity of tissue stress and interstitial flow, the presence of which may promote nonuniform host infiltration.

The mechanisms by which metabolic wastes are cleared from the brain are important for understanding natural brain function and the pathophysiology of several neurological disorders. Recent evidence suggests clearance may occur via perivascular spaces (PVS), annular gaps that exist between cerebral blood vessels and brain parenchyma. We have also developed an MRI-based methodology to visualize PVS and reconstruct the PVS network in the rat brain interior[2]. There is a need to quantify the connectivity of perivascular channels at the tissue level to better understand the physics of PVS flow and to study the effects of abnormalities in these networks with disease. We found an extensive perivascular network that reduces the time scale for diffusive solute clearance from the parenchyma, suggesting that toxic waste clearance may be possible with minimal interstitial flow.

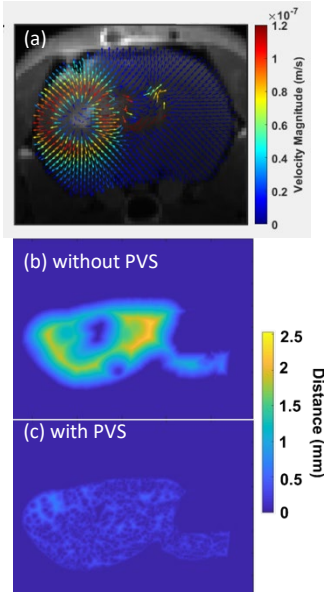

Fig 1. (Top) Predicted velocity field for a tumor bearing rat. (Bottom) Sagittal view of minimum distance between parenchyma and CSF spaces without (b) and with PVS (c).

1. Rey, J. A., Ewing, J. R., Sarntinoranont, M. (2021) A Computational Model of Glioma Reveals Opposing, Stiffness-sensitive Effects of Leaky Vasculature and Tumor Growth on Tissue Mechanical Stress and Porosity, *Biomechanics and Modeling in Mechanobiology,* doi: 10.1007/s10237-021-01488-8
2. Magdoom, K.N., Brown, A., Rey, J., Mareci, T.H., King, M.A., Sarntinoranont, M. (2019) MRI of Whole Rat Brain Perivascular Network Reveals Role for Ventricles in Brain Waste Clearance, *Scientific Reports*, 9:11480, doi: 10.1038/s41598-019-44938-

Malisa Sarntinoranont

About the Presenter. Dr. Sarntinoranont is a Professor in the Department of Mechanical & Aerospace Engineering at the University of Florida. Her research is driven by a vision to develop translational tools for patient-specific therapy. The focus of her lab has been image-based computational models that predict flows, stress and clearance within the brain, spinal cord and tumors. Dr. Sarntinoranont received her undergraduate degree from Georgia Tech. She completed her M.S. and Ph.D. degrees in mechanical engineering at U.C. Berkeley. Her post-doctoral training was at the National Institutes of Health (NIH) in Bethesda, MD. She is a fellow of the American Society of Mechanical Engineers.

INTERSTITIAL FLUID FLOW DURING GLIOMA PROGRESSION

Jenny Munson[1,2], Jessica Cunningham[1], Cora Esparza[1,2]

[1] Fralin Biomedical Research Institute, Virginia Tech, Roanoke, VA, USA
[2] Department of Biomedical Engineering and Mechanics

Abstract. Interstitial fluid flow is characterized as the flow that moves between cells within the extracellular spaces. In the brain, these flows move between the glial and neural cells and are vital to movement of nutrients and waste and potentially contribute to as yet unknown functional outcomes. Glioblastoma is the deadliest brain tumor and is characterized by an invasive phenotype. We and others have linked heightened interstitial fluid flow to glioma invasion in vitro and in vivo. During glioma formation and progression, tumors develop heightened interstitial pressure which drives fluid out into the surrounding parenchyma increasing this interstitial fluid flow directly across invasive regions of tumors. We have developed methods to image and analyze this interstitial fluid flow in and around implanted and naturally occurring glioma across species to better understand the direction, magnitude and nature of these flows in glioblastoma(1,2).

We implanted three different murine gliomas in mice (n=5-8 per group) and imaged using dynamic contrast enhanced MRI with gadolinium contrast agent delivered IV at day 6, 8, and 10 post implantation. Images were taken sequentially and then processed using our published Lymph4D image analysis tool. We analyzed interstitial fluid flow within and around the tumor to determine flow velocity fields. Generally, at early timepoints, the interstitial fluid flow patterns mimic the known and predicted trajectories of fluid flow through the brain (**Fig. 1A,B**), primarily in the ventral to dorsal direction in a coronal slice. As the tumor grew, this flow pattern was disrupted and a more traditional outward flow is seen (**Fig. 1C, D**). Similar outcomes were seen regardless of the implanted model (xenograft of syngeneic).

Analysis of the velocity magnitudes did indicate an increase in velocity of flow at the tumor margins with growth of the tumors. In this presentation, we will discuss these data as well as the natural flows that we observe in non-tumor bearing brains. Further, similar analysis in human glioblastoma from archival patient data. We hypothesize that naturally occurring parenchymal flows may contribute to glioma progression and behaviors prior to the development of tumor-generated pressure gradients and flows.

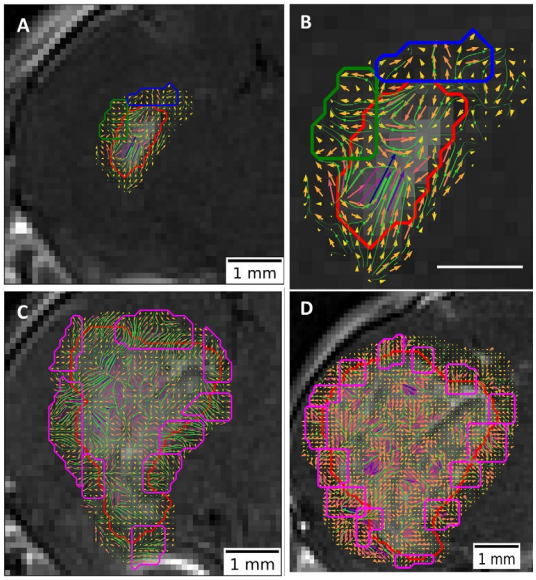

Fig. 1.Interstitial fluid flow in a progressing tumor implanted in a mouse as measured by MRI A) Glioma stem cell line G34 at 6 days post implantation with B) close-up inset showing interstitial fluid flow streamlines. Boxes indicate regions were flow is outward compared to the border of the tumor. Same processing on the same tumor at (C) 8 days and (D) 10 days post implantation indicating progression. Boxes indicating outward flow are now more abundant.

1. Chatterjee K, Atay N, Abler D, Bhargava S, Sahoo P, Rockne RC, Munson JM. Utilizing Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) to Analyze Interstitial Fluid Flow and Transport in Glioblastoma and the Surrounding Parenchyma in Human Patients. *Pharmaceutics* (2021) **13**:212. doi: 10.3390/pharmaceutics13020212

2. Kingsmore KM, Logsdon DK, Floyd DH, Peirce SM, Purow BW, Munson JM. Interstitial flow differentially increases patient-derived glioblastoma stem cell invasion via CXCR4, CXCL12, and CD44-mediated mechanisms. *Integr Biol (Camb)* (2016) **8**:1246–1260. doi: 10.1039/c6ib00167j

Jenny Munson

About the Presenter: Dr. Jenny Munson is an Associate Professor at the Fralin Biomedical Research Institute and Department of Biomedical Engineering and Mechanics at Virginia Tech. Her laboratory develops methods to measure, model, and manipulate interstitial fluid flow in normal and pathological conditions.

Microvessels and Perivascular Space Detection Using MRI

Quan Jiang[1,3], Jiani Hu[2], Yimin Shen[2], E Mark Haacke[2]

[1] Department of Neurology, Henry Ford Health System, Detroit, MI, USA; [2] Department of Radiology and [3]Neurology, Wayne State University, Detroit, MI, USA

Abstract. The current understanding of cerebral waste clearance (CWC) involves cerebrospinal fluid (CSF) participation but the role of the parenchymal vascular system in CWC is unclear. This may be attributed in part to technical difficulties for performing ultra-high detection sensitivity for microvessels and perivascular spaces in whole brain imaging. Conventional MRI is insufficient for investigating microvessels and perivascular spaces in glymphatic and vascular systems. In this talk, we will discuss the superparamagnetic iron oxide-enhanced susceptibility weighted imaging (SPIO-SWI) method in detecting microvessels and perivascular spaces in rats. We will first discuss the optimization sensitivity of this method in detecting microvessels after intravenous (iv) injection of MRI contrast agent (CA). The USPIO-SWI method exhibited its excellent ability to detect small vessels down to about 10 μm diameter in rat brain (Fig. 1)[1]. We will then discuss quantitative evaluation of MRI signal changes in parenchymal veins, arteries, and their corresponding perivascular spaces following intra-cisterna magna (ICM) infusion of CA. Our results show that the SPIO-SWI method with ICM injection of tracer can quantitatively evaluate tracer distributions in parenchymal veins, arteries, and their corresponding perivascular spaces and parenchymal vascular system is likely participating to CWC.

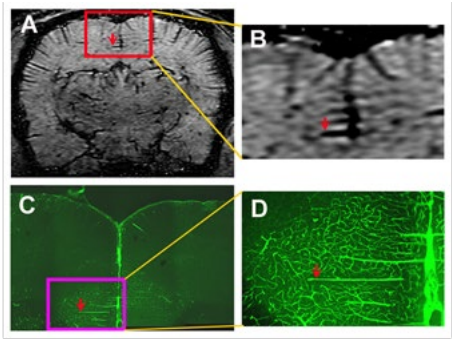

Fig 1. Direct comparison of microvessels between MRI and LSCM: A, a coronal SPIO-SWI images post IV injection of Ferumoxytol. **C,** the corresponding slice of laser scanning confocal microscopy (LSCM). **B** and **D** show enlarged regions indicated by color rectangles in **A** and **C**, respectively. The red arrows indicate position of the target micro vessel.

1. Wang H, Jiang Q, Shen Y, Zhang L, Haacke EM, Ge Y, et al. The capability of detecting small vessels beyond the conventional mri sensitivity using iron-based contrast agent enhanced susceptibility weighted imaging. NMR Biomed. 2020:e4256

Quan Jiang

About the Presenter: Quan Jiang. He received the B.S. degrees in physics from Zhejiang University, Hangzhou, China, in1982 and the M.S. degrees in nuclear physics from Idaho State University, Pocatello, ID, in 1987 and Ph.D. degrees in medical physics from Oakland University, Rochester, MI, in 1991, respectively. Since 1991, he has been with the Department of Neurology, Henry Ford Health System, Detroit, MI, where he is currently a Senior Staff Scientist. Since 2003, he has been with the Department of Neurology of Wayne State University where he is currently a full adjunct Professor. He has published over 140 papers in peer reviewed journals and book chapters. He has served on the study sections of the National Institutes of Health (NIH) and other funding agencies.

ARTERIAL VASODILATION DRIVES CONVECTIVE FLUID FLOW IN THE BRAIN: A POROELASTIC MODEL

Ravi T. Kedarasetti[1], Patrick J. Drew[1], **Francesco Costanzo[1]**

[1] Engineering Science and Mechanics Department, Penn State University, University Park, PA, USA

Abstract. Waste clearance from the brain is tied to fluid motion through the brain. Whether clearance occurs primarily through diffusion or convection is controversial, though it is thought to be much higher during sleep. Neurovascular coupling, as opposed to arterial pulsations, is an attractive candidate for driving flow because of the large brain deformations and significant fluid flow it induces, especially during sleep. Here we report simulations of fluid flows induced by vasodilation into and out of the brain using a poroelastic model [1] (Fig. 1). We model the flow through the extracellular (ECS), subarachnoid (SAS), and paravascular (PVS) spaces via Darcy-Brinkman equations with different permeabilities. The brain was modeled as a very soft poroelastic body. For the simulations we used a custom finite element scheme in COMSOL Multiphysics [2]. Time-dependent arterial wall displacements taken from experimental measurements (Fig. 1(a)) were prescribed as boundary conditions. We examined how dilation amplitude and tissue porosity contributed to convective transport during functional hyperemic events like those found in awake or sleeping mice. A typical pressure/velocity response to a single dilation event $10s$ in duration is shown in Fig. 1(b), demonstrating how arterial dilation can drive convection through the tissue. We found that repetitive dilation events were more effective in driving fluid through the brain if the dilations and tissue porosity (ζ_{Rf}) were larger, as would occur during sleep. Particle trajectories are shown in (c) and (d). Particle distribution over time is quantified in (d), (f), and (g). We found that arteriolar dilations could drive convective flow through the brain radially outward from the arteriole, and that this flow is sensitive to the temporal dynamics of the dilation. Simulations of sleep-like conditions, with larger vasodilations and increased extracellular volume in the brain showed enhanced movement of fluid from the paravascular space into the brain. Our simulations suggest that both sensory-evoked and sleep-related arteriolar dilations can drive convective flow of cerebrospinal fluid from the PVS into the brain tissue around arterioles. This work was supported by NSF Grant CBET 1705854 and R01NS078168 from the NIH to PJD.

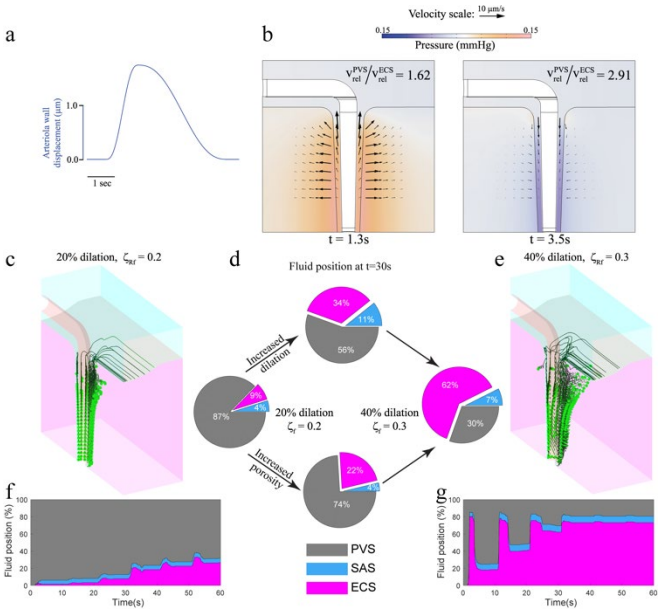

Fig. 1. We consider (b,c,e) a $80 \times 200 \times 200 \mu\mathrm{m}$ region of cortex below the subarachnoid space (SAS) into which an arteriole penetrates. The arteriole is surrounded by a fluid-filled paravascular space (PVS) communicating with the SAS. The whole system is modeled as poroelastic with separate equations for the fluid and solid phases and with position dependent properties. The amounts of fluid and solid are measured by their respective volume fractions.

2. Kedarasetti R, Drew P, Costanzo F (2021). Arterial vasodilation drives convective fluid flow in the brain: a poroelastic model, bioRxiv, DOI: 10.1101/2021.09.23.461603, under review in Fluids and Barriers of the CNS.

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About the Presenter: Francesco Costanzo is a professor in the Engineering Science and Mechanics Department at Penn State and a member of the Penn State Center for Neural Engineering. He also holds courtesy appointments in Mathematics, Mechanical Engineering, and Biomedical Engineering. His primary research interest is the mathematical and numerical modeling of material behavior with a focus on fluid-structure interaction in biomedical applications.

Francesco Costanzo

SESSION D, THURSDAY, JUNE 16TH, 14:45 – 15:10

THE IMPORTANCE OF RESISTANCE TO CSF MOTION AND BRAIN TISSUE MOTION IN CHIARI MALFORMATION SYMPTOMATOLOGY

Francis Loth[1], Rafeeque Bhalia[2], Rouzbeh Amini[1], John Oshinski[3]

[1] Departments of Mechanical and Industrial Engineering and Bioengineering, Northeastern University, Boston, MA, USA
[2] Beth Israel Deaconess Medical Center, Department of Radiology, Harvard Medical School, 330 Brookline Avenue, Boston, MA, USA
[3] Radiology & Imaging Sciences and Biomedical Engineering, Emory University School of Medicine, Atlanta, Georgia, USA

Abstract. Our group has sought to identify biomechanical factors that may be indicative of symptom severity in Chiari malformation (CM) type I. We have studies two biomechanical factors in some detail: 1) resistance to cerebrospinal fluid (CSF) motion in the spinal canal and 2) regional brain tissue motion during the cardiac cycle. We have previously shown that integrated longitudinal impedance (ILI), which is a measure of the unsteady resistance to CSF in the spinal canal and brain tissue motion during the cardiac cycle, is larger for CM subjects compared to healthy controls. In addition, we have shown that both ILI and brain tissue motion for CM subjects decreases after decompression surgery. One recent[1] study examined ILI for patient with and without cough-associated headaches (CAHs). CAHs are thought to be distinctive for CM patients. We used computational fluid dynamics (CFD) to compute patient-specific ILI for CM patients to determine its accuracy in predicting CAH. Fifty-one symptomatic CM patients with cerebellar tonsillar position (CTP) ≥ 5 mm were included in this study. The patients were divided into two groups based on their symptoms (CAH and non-CAH) by review of the neurosurgical records. A receiver operating characteristic (ROC) curve was evaluated for its accuracy in predicting CAH. The ILI for CMI patients with CAH (776 dyn/cm^5) was significantly larger compared to non-CAH (285 dyn/cm^5, p = 0.001). ILI was more accurate in predicting CAH in CMI patients than the CTP when the comparison was made using the area under the ROC curve (0.77 and 0.70, for ILI and CTP, respectively). ILI ≥ 750 dyn/cm^5 had a sensitivity of 50% and a specificity of 95% in predicting CAH. While ILI was more predictive of CAHs than CTP, the difference was less pronounced than expected. A second recent study[2] examined brain tissue motion for 23 CM subjects. The spatially averaged peak tissue displacement reduced by 46% within the cerebellum and by 22% within the brainstem after decompression surgery ($p< 0.001$). Maximum peak displacement, calculated within a circular 30-mm^2 area, decreased by 64% in the cerebellum and 33% in the brainstem ($p< 0.001$). However, no presurgical symptoms demonstrated correlations with brain tissue displacement according to our predefined cutoff that controlled for family-wise error using a Bonferroni correction ($p< 0.0002$). These results indicate that while resistance to CSF motion and brain tissue displacement may play a role in CM symptomatology, they are not sufficient alone to explain the presence of symptoms. Current studies are underway to examine resistance, compliance, and tissue motion together in the prediction of CM symptomatology.

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2. Eppelheimer MS, Nwotchouang BST, Heidari Pahlavian S, Barrow JW, Barrow DL, Amini R, Allen PA, Loth F, Oshinski JN, "Cerebellar and Brainstem Displacement Measured with DENSE MRI in Chiari Malformation Following Posterior Fossa Decompression Surgery," Radiology. 2021 Oct;301(1):187-194. doi: 10.1148/radiol.2021203036. Epub 2021 Jul 27, PMID: 34313469

About the Presenter: Francis Loth received his Ph.D. degree in Mechanical Engineering in the area of biofluids at the Georgia Institute of Technology in 1993. He began his career as a faculty member of the Mechanical Engineering Department at the University of Illinois at Chicago in 1996. In 2008, he moved to The University of Akron in the Department of Mechanical Engineering. In 2022, he moved to Northeastern University in the Departments of Mechanical and Industrial Engineering and Bioengineering. His research area is in the simulation and measurement of blood and cerebrospinal fluid dynamics. He employs both experimental and numerical techniques to better understand the biomechanical forces involved in bypass graft failure as well as in diseases such as atherosclerosis, Chiari malformation, and syringomyelia. He has co-organized several workshops in the area of hemodynamics (2001) and Chiari malformation/CSF (2007, 2008, 2010, 2011 and 2014).

Francis Loth

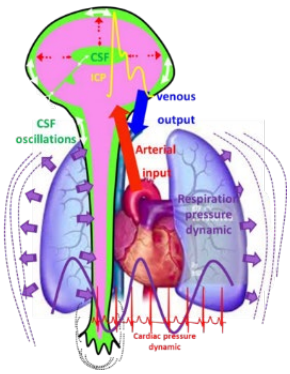
SESSION D, THURSDAY, JUNE 16TH, 15:10 – 15:35

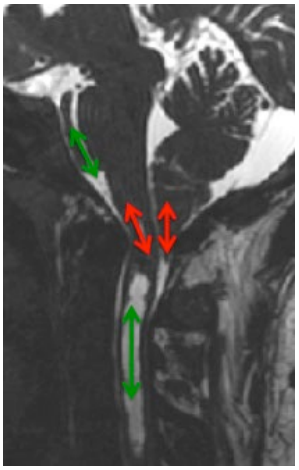
INTRACRANIAL VOLUME DYNAMICS IN ARNOLD-CHIARI SYNDROME

Olivier Balédent[1,2], Catherine Gondry-Jouet[2,3], Serge Metanbou[2,3], Cyrille Capel[2,4].

[1] Image processing department, University hospital, Amiens, France.
[2] Chimère UR 7516, Jules Verne University, Amiens, France.
[3] Radiology department, University hospital, Amiens, France.
[4] Neurosurgery department, University hospital, Amiens, France.

Abstract. The Monro-Kellie doctrine stating that the sum of volumes of brain tissues, cerebrospinal fluid (CSF) and intracranial blood is constant is not true during the cardiac cycle. That means exist an intracranial compliance and finally that not all the intracranial volumes are completely rigid or no compressible. Because venous outflow cannot flush outside the cranium as quick as the arterial flows fill the brain (due to viscosity of blood) exist an increase of the intracranial blood volume during the cardiac cycle. It is well known from healthy population, that CSF, mainly coming from the pontine cistern (few from the ventricles) balances the blood expansion by quickly (small viscosity) flushing in spinal canal. The Foramen Magnum is a crucial pathway and its flow resistance must be as small as possible to avoid a bottling of CSF fluid in this funnel. To quantify these intracranial volume oscillations during cardiac cycle we are using simple 2D cine phase contrast magnetic resonance imaging (PC MRI)[1]. PC MRI applied in the cerebral arteries and venous vessels at the cervical and intracranial level can quantify the arterio venous flow difference during cardiac cycle. Then provide the dynamic of the intracranial blood volume change during cardiac cycle, origin of the CSF movements[2]. PC MRI can also quantify CSF and potential movements of the spine and cerebellar tonsils through the foramen Magnum and the spinal canal[3,4]. The aim of this presentation is to show how Chiari syndrome affects intracranial dynamic of the neuro fluids and develop abnormal oscillations of neuro axis. We will show in majority of Chiari patients that the main cerebral venous outflows pathways were reduced. That CSF flows in the spinal canal is normal. This paradox is due to the neuroaxis back and forth movement that act as a piston trough the Foramen Magnum. We will also show how bone surgery reduces this abnormal movement of the neuroaxis.





In conclusion the results show that cerebellar tonsils position could results not only for malformation but also from an alteration of the intracranial compliance mechanism that normally balance the arterial cerebral volume expansion during the cardiac cycle to avoid too large intracranial pressure amplitude increase. Such abnormal movements of the neuro axis could alter integrity of the spine fibers, faille it and finally conduct to syringomyelia cavity development.

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2. *Balédent O, Henry-Feugeas MC, Idy-Peretti I. Cerebrospinal fluid dynamics and relation with blood flow: a magnetic resonance study with semiautomated cerebrospinal fluid segmentation. Invest Radiol. 2001 Jul;36(7):368-77.*
3. *Williams G, Thyagaraj S, Fu A, Oshinski J, Giese D, Bunck AC, Fornari E, Santini F, Luciano M, Loth F, Martin BA. In vitro evaluation of cerebrospinal fluid velocity measurement in type I Chiari malformation: repeatability, reproducibility, and agreement using 2D phase contrast and 4D flow MRI. Fluids Barriers CNS. 2021 Mar 18;18(1):12.*
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Olivier Belédent

About the Presenter: Olivier Balédent, PhD in the area of biophysics & radiology. He is currently assistant professor, heading the medical image-processing department in Amiens 'University Hospital in France. He is member of the CHIMERE UR 7516 research team. He is director of the animal MR department of the Jules Verne University. Vice president of the *Imaging neurofluids* study group in the international society of magnetic resonance in medicine. He passed his Phd in 2001 at Jules Verne University. The thesis subject was about CSF and cerebral blood flows imaging using MRI. Now with clinicians he continues to develop CSF researches in clinical practice. He is also Biophysics' teacher at the medical school of Amiens.

SESSION D, THURSDAY, JUNE 16TH, 15:35 – 16:00

TACHYCARDIA AND HYPERTENSION ENHANCE CSF FLOW OUT OF THE SPINAL CORD

Marcus Stoodley,[1] Shinuo Liu,[1] Lynne E. Bilston,[2] Sarah J. Hemley[1]

[1] Faculty of Medicine, Health and Human Sciences, Macquarie University, NSW 2109, Australia
[2] Neuroscience Research Australia, Prince of Wales Clinical School, University of New South Wales, NSW 2031, Australia

Abstract. Disruption of cerebrospinal fluid (CSF)/interstitial fluid (ISF) exchange in the spinal cord is likely to contribute to central nervous system (CNS) diseases that involve abnormal fluid accumulation, including spinal cord oedema and syringomyelia. However, the physiological factors that govern fluid transport in the spinal cord are poorly understood. The aims of this study were to determine the effects of cardiac pulsations and respiration on tracer signal increase, indicative of molecular movement following infusion into the spinal cord grey or white matter. In Sprague Dawley rats, physiological parameters were manipulated such that the effects of spontaneous breathing (generating alternating positive and negative intrathoracic pressures), mechanical ventilation (positive intrathoracic pressure only), tachycardia (heart atrial pacing), as well as hypertension (pharmacologically induced) were separately studied. Since fluid outflow from the spinal cord cannot be directly measured, we assessed the molecular movement of fluorescent ovalbumin (AFO-647), visualised by an increase in tracer signal, following injection into the cervicothoracic spinal grey or white matter. Tachycardia and hypertension increased AFO-647 tracer efflux, while respiration did not. Following AFO-647 tracer injection into the spinal grey matter, increasing blood pressure and heart rate resulted in increased tracer movement away from the injection site compared to the hypotensive, bradycardic animals (hypertension: $p = 0.05$, tachycardia: $p < 0.0001$). Similarly, hypertension and tachycardia produced greater movement of AFO-647 tracer longitudinally along the spinal cord following injection into the spinal white matter ($p < 0.0001$ and $p = 0.002$, respectively). Tracer efflux was strongly associated with all blood vessel types. Arterial pulsations have profound effects on spinal cord interstitial fluid homeostasis, generating greater clearance than respiration, demonstrated by increased craniocaudal CSF tracer movement in the spinal cord parenchyma.

Marcus Stoodley

About the Presenter: Professor Stoodley is head of neurosciences at Macquarie University. In addition to his clinical interests in neurovascular disease and CSF disorders, Professor Stoodley heads the neurosurgery research team at Macquarie University. This is one of the largest neurosurgery research groups in Australasia, with world-leading research efforts in syringomyelia and CSF physiology, and in the development of new treatments for brain AVMs. This work has attracted over $5 million in research funding, including support from Australia's major medical research funding body the NHMRC and The Column of Hope, a US-based organization dedicated to advancing the understanding and treatment of syringomyelia. He has produced more than 160 publications and has supervised 17 PhD projects. He has delivered over 90 invited lectures at national and international scientific meetings.

PLENARY LECTURE, FRIDAY, JUNE 17TH, 9:00 – 10:00

SPINAL CORD MOTION DISORDER: INTRODUCTION OF A NOVEL CONCEPT

Petra M Klinge, MD PhD

Professor of Neurosurgery, Director of Pediatric Neurosurgery and the CSF center of the brain and spine

Rhode Island & Hasbro Children's Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Abstract. The spinal cord (SC) is elastically supended and floating in CSF within the dural sac to protect the delicate nervous structures against spine movement related forces. In addition, the dural sac is not tightly connected to the bony skeleton but also suspended by extradural ligaments, particularly in areas where major spine movements may occur, for example in the cranio-cervical junction (CCJ).

The most acknowledged structures of intradural SC suspension are the denate ligaments and the exiting ventral and dorsal nerve roots that provide and internal anchor of the spinal cord to the dura. The role of extradural ligamentous suspension is less studied. We have recently reported the role of myodural-bridge-ligaments (MDBs) for stabilizing the spinal cord during head and neck movements at the cranio cervical junction (CCJ). We have found that in hEDS the MDBs are structurally diseased and have shown by in-vivo ultrasound that this is associated with an impaired motion control of the SC during head and neck movements. We theorized that such a "spinal cord motion disorder" can cause symptoms of a CCJ instability, i.e., head and neck pain even without bony CCJ instability. Notably, the MDBs have also been theorized to promote CSF movement and in essence act as a pump to aid in pushing CSF back and forth. It is not known whether this function is impaired in hEDS.

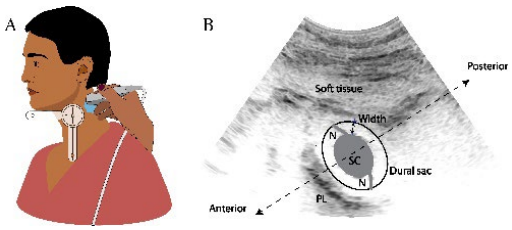

Fig. 1. Positioning of the ultrasound probe at the neck to visualize the spinal cord movements at the CCJ. (N=nerve roots, SC=spinal cord, Width of subarachnoid space, PL= posterior ligament).

The filum terminale is another largely understudied spinal cord suspension ligament. We performed histological and ultrastructural studies of surgical FT specimens in patients with tethered cord syndrome. In addition we studied the elastic properties of the FT applying biomechanical testing. Comparing the findings of patients with and without hEDS, we found in hEDS the FT structurally affected and the elastic properties impaired. This pathology may result in stretch injury to the SC causing a clinically manifest TCS. Our findings build the rational for FT surgery in TCS with hEDS co-morbidity even without a radiologically confirmed low lying conus.

We suggest a novel pathological entity, i.e. "spinal cord motion disorder", which may contribute to the understanding of a variety CSFdisorders and diseases, i.e. Chiari, Syringomyelia and tethered cord syndromes.

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Petra Klinge

About the Presenter: Dr. Klinge practices in complex adult and pediatric hydrocephalus as well as developmental cerebrospinal fluid disorders, such as spina bifida, Chiari malformation, tethered cord, patients with connective tissue disorders and associated spinal fluid disorders including syringomyelia and occult tethered cord syndrome. Her scientific interests focus on the novel understanding and development of advanced techniques for diagnosing and treatment of disorders of the cerebrospinal fluid circulation and the neurodegenerative diseases.

Deep breathing - one coupling mechanism of CSF and venous flow dynamics

Jost M. Kollmeier[1], Lukas Guerbuez-Reiss[2], Prativa Sahoo[2], Simon Badura[2], Ben Ellebracht[2], Mathilda Keck[2], Jutta Gärtner[2], Hans-Christoph Ludwig[3], Jens Frahm[1,4], **Steffi Dreha-Kulaczewski[2]**

[1] Biomedizinische NMR, Max-Planck-Institut für multidisziplinäre Naturwissenschaften, Goettingen, Germany

[2] Department of Pediatrics and Adolescent Medicine, University Medical Center Goettingen, Germany

[3] Department of Neurosurgery, Division of Pediatric Neurosurgery, University Medical Center Goettingen, Germany

[4] German Center for Cardiovascular Research, partner site Goettingen, Germany

Abstract. Venous system pathologies have increasingly been linked to clinically relevant disorders of CSF circulation whereas the exact coupling mechanisms still remain unknown. In this work, flow dynamics of both systems were studied using real-time phase-contrast flow MRI in 16 healthy subjects during normal and forced breathing (breathing protocol in bottom row of Fig. 1).

Regions of interest (ROIs) for the analysis of CSF dynamics were placed in the aqueduct (Aqd) and spinal subarachnoid spaces at C3 and L3. For corresponding venous flow ROIs were drawn around internal jugular veins (IJV) and inferior vena cava (IVC). The spinal epidural venous plexus forms prominent epidural veins (EV) at C3 which were selected. The lumbar venous plexus is a spacious mesh rendering epidural vessels less well identifiable and ROIs were defined around epidural flow signals detectable ventral to the CSF space.

The central observation of this work is the fact that the dynamics of CSF and venous blood flow vary distinctly between normal and forced breathing and thus confirm the strong dependence of both systems on respiration (s. Fig. 1). In contrast to normal breathing where cardiac driven frequency components prevail, the beginning of deep respiration causes immediate adherence of fluid dynamics to that driving force. The prompt transition from normal to forced breathing causes a switch from cardiac- to respiration-related dynamics in all positions except for C3-CSF. Moreover, forced inspiration elicits a distinct upward surge of CSF from the lumbar region up to the intracranial Adq in line with previous findings. In contrast, forced expiration leads to reversed, downward flow. Venous outflow from the head/neck region is also modulated by forced respiration which so far has only been demonstrated for the cervical epidural veins. Simultaneously, the steady venous flow from the lower body up towards the heart abates at the onset of forced inspiration and rises quickly afterwards throughout expiration.

In conclusion forced respiration leads to increases and a prompt synchronization of flow dynamics in CSF and venous systems. The lumbar caval and epidural venous upward surge during free breathing abates with the onset of forced inspiration and rises during ensuing exhalation – a pattern opposite to that of venous flow in the upper body part. Spinal and intracranial CSF, on the other hand, move uniformly upwards during forced inhalation as previously described. Our results provide evidence that deep respiration couples interdependent venous and brain fluid flow – most likely mediated by intrathoracic and intraabdominal pressure changes. Further insights into the tight interplay between CSF and venous fluid dynamics will expand our understanding of human diseases caused by CSF flow disturbances such as hydrocephalus and facilitate the development of more specific therapeutic options.

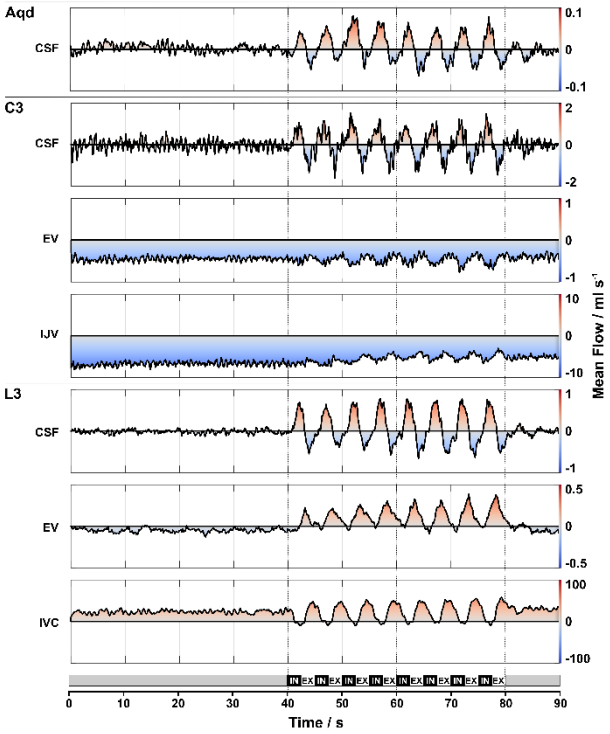

Fig. 1: Mean CSF and venous flow.
Color-coded mean flow rates (ml s^{-1}) of CSF and venous blood averaged across subjects during 90 s breathing protocol (bottom). **Normal breathing (0-40 s):** low CSF flow with cardiac pulsatility. Venous flow in C3 EV and IJV remains constantly negative (blue). IVC shows upward (red) flow. Mean L3 EV flow is close to zero with a tendency towards the downward direction (light blue). **Forced breathing (40-80 s):** synchronous flow of CSF and venous blood following respiratory modulations. CSF moves upwards with IN in all ROIs (red) and downwards during EX (blue). Venous blood in the vessels at C3 shows downward flow with only small modulations. In L3 IVC flow modulations are more pronounced i.e. assuming a decrease during IN and an increase during EX. Flow in L3 EV yields a similar behavior. **Normal breathing (80-90 s):** rapid return of CSF and blood flow to the initial pattern. IN = inspiration, EX = expiration.

Steffi Dreha-Kulaczewski

About the Presenter: Steffi Dreha-Kulaczewski is a pediatric neurologist and focuses on hydrocephalus and other disorders of disturbed CSF circulation in children as well as on childhood leukodystrophies. Research activities comprise application of novel quantitative MR-techniques i.e. real-time flow MRI to unravel underlying pathophysiology of perturbed CSF dynamics giving raise to hydrocephalus, pseudotumor cerebri, and syringomyelia. Moreover, the studies aim at the establishment of diagnostic markers or parameters for evaluating therapy effects.

SESSION E, FRIDAY, JUNE 17TH, 10:25 – 10:50

OSCILATION WITHIN THE NEUROFLUIDS

Noam Alperin, PhD

[1] Department of Radiology, University of Miami, Miami, FL, USA

Abstract. Similar to the discovery of the CSF, a decades-long process, so were the efforts to elucidate the origin of the CSF oscillations. The link between the CSF and the cardiovascular oscillations was first observed in the 1940s owing to the synchronization between the blood and CSF pressures oscillations [1]. Regardless of numerous studies that utilized simultaneous measurements of the pulsatile CSF and blood pressures, the origin of the CSF oscillation remained elusive. The introduction of velocity imaging by MRI in the late 1980s provided a new perspective into the CSF oscillations through measurements of volumetric flows, which obey conservation laws. These measurements revealed that the momentary difference between the transcranial arterial inflow and the venous outflow is the driving force of the cranio-spinal CSF pulsation (Fig 1c), which is further modulated by the intracranial compliance (ICC) [2].

The above observations have led to the development of a noninvasive method to measure ICP from MRI measurements of blood and CSF volumetric flow to and from the cranium (Fig 1b), the mono-exponential relationship between the intracranial volume (ICV) and ICC, and the inverse relation between ICC and ICP [3]. The ICC is the ratio of the maximal changes in ICP and the ICV during the cardiac cycle [3].

An obstacle for the adaptation of this methodology is the notion that, as per the Monro–Kellie doctrine, the ICV is constant. Measurement of the small change in ICV are indeed challenging, but can be done reliably following tips provided in a recent communication "Does the brain has mechanical compliance" [4].

Another obstacle is chronic skepticism of expert NIH reviewers. For example, "if the {MRICP} method was really working, it would have been widely used by now" [5]. While there is no scientific response to such criticism, there are now successful independent implementations of the MRICP method such as the recent work by Tsai et al who applied the method in spontaneous intracranial hypotension [6].

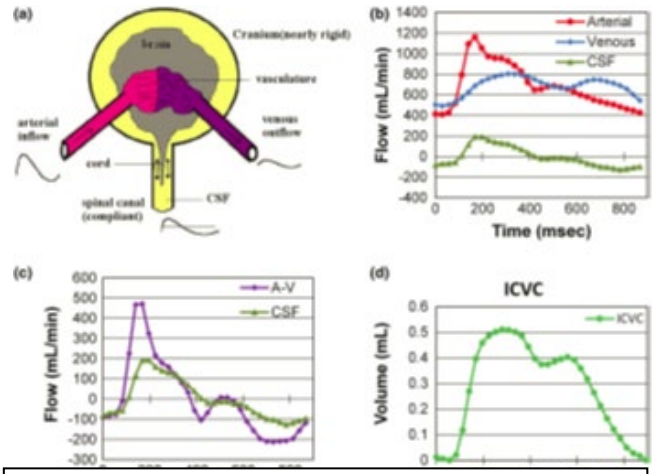

Fig. 1**a** A simplified representation of the cranio-spinal system and the cranial inlets and outlets. **b** Volumetric flow rate waveforms of the arterial inflow, venous outflow, and the cranio-spinal CSF flow. **c** The CSF flow waveform plotted with respect to the arterial minus venous flow waveform. The fact that these two waveforms are not identical implies that the ICV is not constant. **d** The intracranial volume change during the cardiac cycle.

Oscillations of CSF flow in another site, the aqueduct, will also be covered. Unlike the cranio-spinal CSF flow, the aquductal CSF flows only within the cranium and thus does not modulate the ICV or the ICP.

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2 Alperin N, Vikingstad EM, Gomez-Anson B, Levin DN. Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. Magnetic Resonance in Medicine 1996; 35: 741-754.
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4 Alperin N. (2020) Does the brain have mechanical compliance? Magnetic Resonance Materials in Physics, Biology and Medicine
5 Linninger A (2017) NIH summary review 6. Tsai Y-H, Chen H-C, Tung H (2018) Noninvasive Assessment of Intracranial Elastance and Pressure in Spontaneous Intracranial Hypotension by MRI, J. MAGN. RESON. IMAGING 2018;48:1255–1263

Noam Alperin

About the Presenter: Noam Alperin, PhD, is a professor of radiology and biomedical engineering at the university of Miami and the head of the physiologic imaging and modeling lab. He completed his graduate training at the University of Chicago and since has been focusing on the role of CSF oscillations is a wide range of applications including Chiari Malformations, IIH, long duration spaceflights, and sleep.

INTRACRANIAL PRESSURE IN THE SUBARACHNOID SPACE AND LATERAL VENTRICLE OF PIGMENTED RATS

Christopher L. Passaglia[1,2], Cesar Hernandez Isidro[1]

[1] Department of Medical Engineering, University of South Florida, Tampa, FL, USA
[2] Department of Ophthalmology, University of South Florida, Tampa, FL, USA

Abstract. There is growing evidence that intracranial pressure (ICP) plays a role in glaucoma since the lamina cribrosa of the optic nerve head is exposed to intraocular pressure (IOP) on one side and ICP on the other. To better understand this putative role, ICP dynamics in different cerebrospinal fluid compartments and their effects on IOP were investigated in anesthetized and conscious adult Brown-Norway rats. Animals were anesthetized for up to 24 hours via intravenous ketamine infusion as ventricular ICP (vICP), subarachnoid ICP (sICP), and/or IOP were concurrently recorded with a vented screw in the skull, 25-gauge needle in a cerebral ventricle, and 33-gauge needle in the anterior chamber of one eye, respectively. In some experiments, vICP was altered by varying the height of a fluid reservoir connected via a three-way stopcock to the ventricle needle. Data were analyzed in terms of means ± standard deviations and cross correlations. Records were separately highpass- filtered and lowpass-filtered with a cutoff frequency of 0.1 Hz to quantify correlation coefficients and lag times of fast and slow ICP fluctuations, respectively. sICP was continuously recorded with a custom wireless telemetry device from conscious animals housed under a 12-hr light-dark cycle The device was attached to a jacket worn by an animal and connected by fluid-filled tubing to a vented screw in the skull or custom head mount containing a tiny cannula implanted in the subarachnoid space. vICP, sICP, and/or IOP were simultaneously recorded in 10 anesthetized rats. Mean vICP over a one-hour period was 5.0 ± 0.7 mmHg (n = 10). It differed by 0.2 ± 1.0 from sICP, which was not significant (n = 3, p < 0.01). IOP was observed to increase in half of the animals by 4.1 ± 4.0 mmHg (n = 5, p = 0.08) after raising vICP by 10 mmHg. sICP increased as well in all animals tested (n = 3). The increase was equal to vICP elevation (9.8 ± 1.0 mmHg, p < 0.01) and exhibited multiple time constants. Cross correlation of vICP and sICP records (Fig. 1) revealed that fast fluctuations were highly correlated (R = 0.88) with approximately zero lag time. Slow fluctuations were also highly correlated (R = 0.89) with zero lag time in two animals and vICP leading sICP by 1.7 s in one animal. ICP was successfully recorded round-the-clock for 3 to 28 days in 3 conscious rats. All animals exhibited a diurnal ICP rhythm. Mean ICP was 5.2 ± 1.8 mmHg during the light phase and 12.3 ± 4.2 mmHg during the dark phase (p < 0.03). We conclude that mean ICP is nearly identical in the subarachnoid space and lateral ventricle of rats. sICP recordings are therefore a viable alternative to vICP recording in conscious animals since the brain is not penetrated by a cannula. ICP variance will, though, be filtered to some degree by the multi-compartmental sICP response dynamics. We also found that ICP varies diurnally, swinging significantly higher during the animal's waking hours. Since we have previously shown that IOP is also higher at night, we conclude that translaminar pressure is relatively stable throughout the day in healthy eyes.

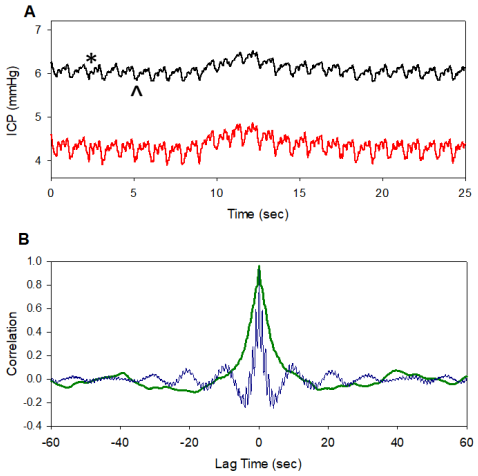

Fig. 1. **(A)** Concurrent recording of sICP (red) and vICP (black) in an anesthetize rat (20 Hz sample rate). Cardiac and respiratory components can be seen as fast fluctuations of 4 Hz (*) and 1 Hz (^), respectively. **(B)** Cross correlogram of low (green) and high (blue) pass filtered records reveals slow synchronous fluctuations of < 0.1 Hz.

Christopher L. Passaglia

About the Presenter: Dr. Christopher Passaglia is a Professor and Associate Chair of Biomedical Engineering at the University of South Florida. He directs the Ocular Neuroscience & Neuroengineering Lab, which uses electrophysiological, computational, instrumentational, and psychophysical methods to investigate the neural basis of vision and engineer novel technologies for eye and glaucoma research.

SIMULATING GLYMPHATIC CLEARANCE IN SLEEP

Kent-Andre Mardal[1,2], Per Kristian Eide[4], Geir Ringstad[3], Marie Rognes[2], Vegard Vinje[2], Bastian Zapf[1]

[1] Department of Mathematics, University of Oslo, Norway
[2] Scientific Computing Department, Simula Resarch Laboratory, Oslo, Norway
[3] Neuroimaging Research Group, Radiology, Oslo University Hospital, Oslo, Norway
[4] Neurovascular & Cerebrospinal Fluid Research Group, Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

Abstract. The glymphatic system [1] promotes distribution and removal of solutes from the brain through interaction with the cerebrospinal fluid in the subarachnoid space. In [2] it was shown that the clearance was particularly active during sleep in mice. It has only recently been shown that also in humans, that the MRI contrast gadobutrol transport and clearance is altered when sleep-deprived are compared with people that slept [3]. In this study we will assess, in a patient-specific manner, the added advection, clearance, and dispersion involved in the glymphatic system through computer simulations. We use the finite element method in order to discretize and compare the results of a standard diffusion equation c.f. e.g. [4,5] with that predicted by optimal mass transport [6]. Our results suggest that the distribution of gadobutrol in the 48 hours after intrathecal administration cannot be explained by extra-cellular diffusion alone, but that reasonable fits can be obtained if added diffusion (such as dispersion), clearance, and or advection is added.

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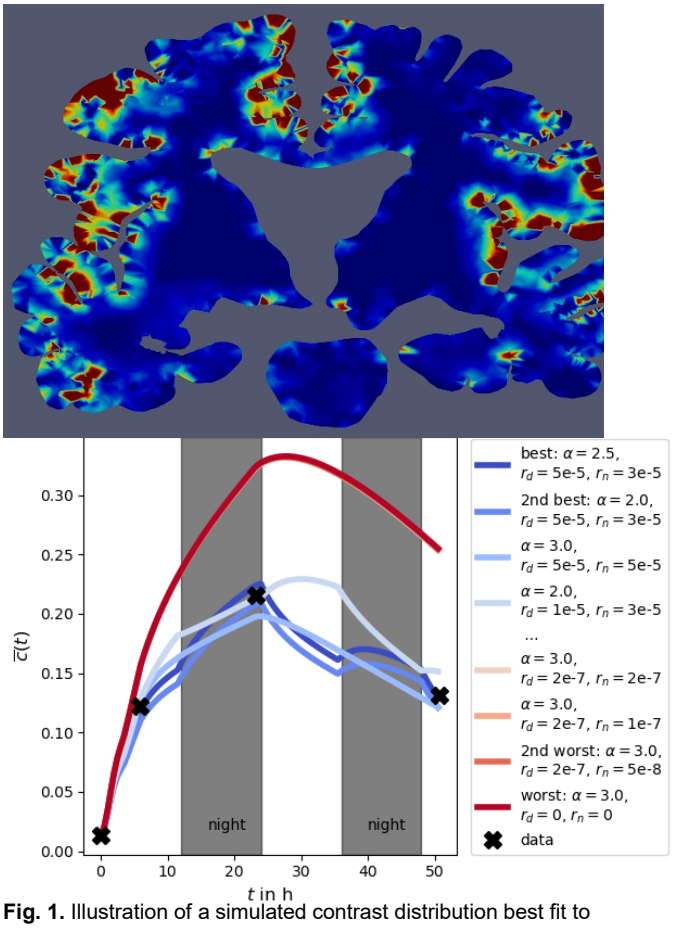

Fig. 1. Illustration of a simulated contrast distribution best fit to the MRI image (top). Quantification of different clearance and diffusion parameters, and a comparison with data (bottom).

Kent-Andre Mardal

About the Presenter: Kent-Andre Mardal is a Professor at the University of Oslo and Adjunct Scientist at Simula Research Laboratory. His scientific interests include finite element methods, computational mechanics, interstitial and cerebrospinal fluid flow in association with the Chiari I malformation, syringomyelia, and hydrocephalus, Alzheimer´s disease and sleep.

SPATIAL AND TEMPORAL DISTRIBUTION PATTERNS OF CSF-ENTRAINED SUBSTRATES AFTER INFUSION INTO ONE LATERAL VENTRICLE

Tavarekere N. Nagaraja[1], Joseph D. Fenstermacher[2]

[1] Dept. of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA

[2] Dept. of Neurological Surgery, State University of New York, Stonybrook, NY, USA

Abstract. The distribution and clearance of radiolabeled sucrose (^{14}C-sucrose)[1] and ^{14}C-polyethylene glycol (PEG), both extracellular distributors and reference tracers; soluble amyloid β peptide-1-40 (^{125}I-saβ)[2]; and insulin-like growth factor-1 (^{125}I-IGF-1)[3] from 3 to 90 min after intraventricular injection were studied in normal, male Sprague-Dawley rats. Briefly, one femoral artery was cannulated in anesthetized rats and their heads affixed in a stereotactic frame. Using standard atlas coordinates, a small volume of normal saline (0.5-1.0µl @ 1µl/min) containing the radiotracer was infused into one lateral ventricle. Timed arterial blood samples were obtained immediately after the infusion began. They were centrifuged and plasma radioactivity measured. At prescribed times, rats were decapitated, and the heads snap frozen by dropping into 2-methylbutane cooled to -40°C using dry ice. The frozen brain with frozen meninges and CSF in place were sectioned and autoradiographic images that spanned the rostro-caudal brain, along with appropriate standards, were obtained[1,2,3]. These data were analyzed with an image analysis system (model MCID; Imaging Research). Radioactivity in liver, kidney and urine were also measured.

Results showed that the CSF-borne passage of the radiotracers shared some common features and also exhibited some unique features for each. Their movement within the ventricles was swift, but their distribution into the subarachnoid spaces varied. Flow of radiotracer was rapid within ventricular system and surprisingly also into the subarachnoid space and cisterns. The latter occurred via the velum interpositum and the superior medullary velum. The subsequent distribution of, for example, ^{14}C-sucrose, was sparse over the cerebral and cerebellar cortices, although such flux at several places was restricted by a thick, multilayered glia limitans. The CSF-to-tissue flux was relatively free and seemingly concordant with simple diffusion. After 1 hour radiotracer was virtually absent from the subarachnoid system with the exception of the perivascular spaces of pial arterioles. In contrast and of interest to amyloid deposition in brain, 30% of ^{125}I-saβ was cleared into blood by 3.5 min after infusion, with another 30% over the next 6.5 min. Paralleling this, the blood, urine and tissue levels of ^{125}I-saβ rose over 3.5-10 min after infusion. Little ^{125}I-saβ was seen in the brain parenchyma, which suggests an efficient clearance mechanism in normal brain (compared to PEG), but the pial arterial vessels still retained it for longer durations. As to movement through the ventricular system, ^{125}I-IGF-1 had spread from the infused lateral ventricle into and through the third and fourth ventricles in the first 5 min. At this time, 25% of the infused IGF-1 had disappeared from the CSF-brain-meningeal system. The plasma concentration of cleared material was, however, very low from 2 to 9 min and only began to rise markedly after 20 min. This delay between loss and gain plus the lack of radiotracer in the cortical subarachnoid space suggested that much of the ^{125}I-IGF-1 was cleared into blood via the cranial and/or spinal nerve roots and their associated lymphatic systems rather than periventricular tissue and arachnoid villi. These data describe some novel pathways of CSF flow and substrate-dependent clearance and distribution patterns in normal brain from the CSF. Whether they are adversely affected in pathologic conditions needs to be investigated.

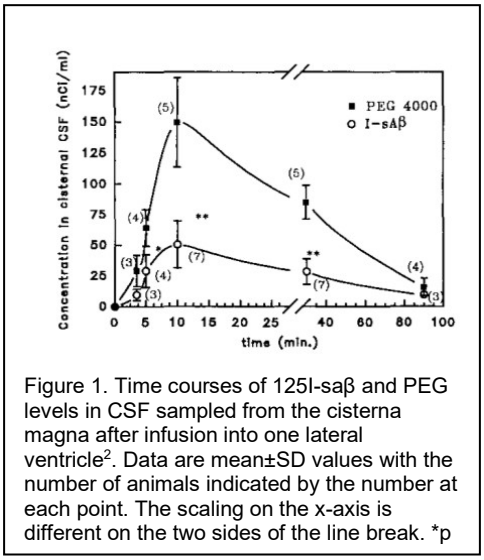

Figure 1. Time courses of 125I-saβ and PEG levels in CSF sampled from the cisterna magna after infusion into one lateral ventricle[2]. Data are mean±SD values with the number of animals indicated by the number at each point. The scaling on the x-axis is different on the two sides of the line break. *p

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"Raj" Nagaraja

About the Presenter: Dr. Nagaraja is a research scientist at the Dept. of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA. His areas of work include: cerebrovascular function in animal models of primary and metastatic brain tumors and in animal models of stroke, traumatic brain injury; CSF flow and its interactions with brain interstitium in normal and hydrocephalic brain; brain drug delivery. Preferred investigative tools are *in vivo* imaging techniques such as MRI and DCE-MRI, that are followed up by terminal gold standard techniques of quantitative autoradiography, histopathology, and fluorescence microscopy.

EVALUATION OF PERISTALSIS AS A DRIVER OF PERIVASCULAR FLOW

M. Keith Sharp

Department of Mechanical Engineering, University of Louisville, Louisville, KY, USA

Abstract. Pulsatile flow in periarterial channels around arteries in the subarachnoid space has been measured [1], but observing flow around penetrating arteries remains a challenge. Pulsatility suggests peristalsis as a candidate mechanism driving the flow. However, the effectiveness of peristalsis in creating mean flow diminishes exponentially as the amplitude of wall motion becomes small, as it is in the periarterial space. Therefore, another mechanism may be required to match the measured flow. Possibilities evaluated here are 1. Peristalsis alone in an open channel, 2. Peristalsis in an open channel with an additional steady pressure gradient, and 3. Peristalsis in a channel containing flexing structures that present greater resistance to reverse flow.

The analytical solution of Jaffrin & Shapiro [2] was applied for peristalsis and steady pressure gradient. This 2D solution is for long wavelength and channel length much longer than the wavelength. Because artery segments between branches of the cerebral vasculature are shorter, this solution likely represents an upper bound on the mean flow caused by peristalsis alone. The Jaffrin and Shapiro solution was extended to include the directional flow resistance of cylinders that are aligned with the channel for forward flow and are perpendicular to the channel for reverse flow. The concentration of cylinders was adjusted to simultaneously match the observed mean flow and amplitude of oscillatory flow.

With the experimentally measured inner wall amplitude ratio of 0.01 [1] for an open channel, the mean flow was ~10x too large (purple circle on Fig. 1) and the oscillatory amplitude was ~1000x too great. Note that motion of the outer wall was not measured, which would tend to reduce the flows. When the wall amplitude was decreased to match the measured oscillatory flow, there was insignificant mean flow (black square). However, when either a pressure gradient of 0.78 mmHg/m or a small concentration (1.27E-10 m/m^3) of cylinders was added, both the oscillatory and mean flows could be matched to the experiments (right-hand ends of the green and red curves). These results support the need for a mechanism other than peristalsis to create mean flow in periarterial channels.

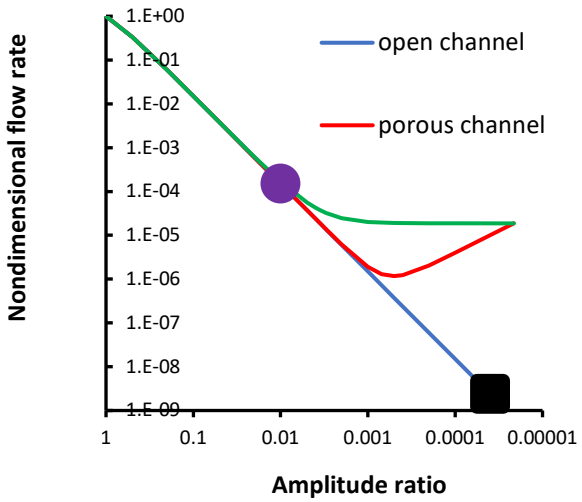

Fig. 1. Mean flow rate versus wall displacement to gap ratio. Blue curve – peristalsis alone in an open channel, green curve – peristalsis with steady pressure gradient, red curve - peristalsis with flexing flow resistors, purple dot – measured amplitude ratio, black square – measured oscillatory flow.

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2. Jaffrin MY & Shapiro AH. Peristaltic pumping. *Ann Rev Fluid Mech* 3:13–36, 1971.

M. Keith Sharp

About the Presenter: Keith Sharp is an ASME Fellow and Emeritus Professor at the University of Louisville. He received Bachelors, Masters and Doctor of Science degrees from the University of Cincinnati, Colorado State University and the Massachusetts Institute of Technology, respectively. His research interests span flow and transport in biological systems, including cardiovascular devices, blood rheology and hemolysis, cardiovascular system modeling, and cerebrospinal and interstitial fluid. He recently built the first Ambient House, which is heated and cooled entirely by ambient energy.

SESSION G, FRIDAY, JUNE 17TH, 14:00 – 14:25

ASSOCIATION BETWEEN PULSATILE COMPONENTS OF CEREBRAL BLOOD FLOW AND INTRACRANIAL PRESSURE IN PATIENTS WITH SUSPECTED HYDROCEPHALUS

A. Pelah[1], A. Kazimierska[2], C. Mataczynski[3], A. Ziolkowski[2], M. Kasprowicz[2], M. Czosnyka[1,4], Z. Czosnyka[1]

[1] Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom

[2] Department of Biomedical Engineering, Wroclaw University of Science and Technology, Wroclaw, Poland

[3] Department of Computer Engineering, Wroclaw University of Science and Technology, Wroclaw, Poland

[4] Institute of Electronic Systems, Warsaw University of Technology, Warsaw, Poland

Abstract. The relationship between cerebral blood flow and intracranial pressure can vary depending on pathology. We aimed to assess this relationship in suspected hydrocephalus by analyzing the association between the cerebral blood flow velocity (CBFV) pulse waveform, as measured by transcranial doppler ultrasonography, and the intracranial pressure (ICP) waveform. The dataset used was comprised of 29 recordings, each from a patient undergoing a cerebrospinal fluid (CSF) infusion study, in which ICP and other vital signs are measured as saline is infused into the lumbar space, creating a rise in ICP. The test allows the clinicians to assess common CSF dynamics such as resistance to CSF outflow and elasticity. Using this dataset, we assessed the relationship between the CBFV pulse amplitude ($CBFV_{amp}$) and the ICP pulse amplitude (ICP_{amp}), each calculated using a fast fourier transform, as well as other components of the waveforms such as mean values. We found a moderate non-linear correlation between ICP_{amp} and $CBFV_{amp}$ (spearman correlation coefficient of 0.4) in a setting in which ICP is directly influenced by a discrete increase in the volume of CSF without hemogenic components, as is the case in refractory intracranial hypertension or plateau waves (ICP A waves). The findings of this study provide further insight into the relationships between intracranial pressure, cerebral blood flow, and cerebral fluids volume balance.

About the Presenter: Adam Pelah is a 2nd year PhD candidate in the Department of Clinical Neurosciences, University of Cambridge, working under the supervision of Prof. Marek Czosnyka. His current research interests include studies on intracranial pressure and cerebral blood flow in various pathologies, as well as potential machine learning applications in neurosurgery. Previous research placements included machine learning and data analysis applications in biomechanics at the Clinical Gait and Movement Laboratory, Cambridge University Hospitals, work which was published and presented at the IET Human Motion and Analysis Conference in London, 2019. Adam holds a Bachelor of Science in Computational Biology and Computer Science from Florida State University, where he also worked on computational genomics with Dr. Jonathan Dennis.

Adam Pelah

QUANTITATIVE STUDY INTO THE PATHOPHYSIOLOGY OF HYDROCEPHALUS

Anthony Podgoršak[1], Fabian Flürenbrock[2], Leonie Korn[2], Nina Trimmel[3], Miriam Weisskopf[3], Marianne Schmid Daners[1]

[1] Product Development Group Zurich, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland
[2] Institute of Dynamic Systems and Control, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland
[3] Division of Surgical Research, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Abstract. Shunt systems used today to treat hydrocephalus have not changed notably in more than 70 years. This stagnation would not be an issue if shunts were a stellar treatment option, but there is consensus in the field that better treatments are needed. However, before these novel treatments can be designed, a deeper quantitative understanding of physiology and hydrocephalus pathophysiology is required. To this end, we investigate the influence of dynamic pressure and volume variations in the craniospinal, arterial, venous, and peritoneal spaces, and their interactions with each other via acute and chronic ovine in-vivo trials.[1,2] Recording all data simultaneously, the communication between these spaces is quantified in four discrete phases: physiologic acute, physiologic chronic, pathologic acute, and pathologic chronic.

The physiologic acute phase investigated cerebrospinal and adjacent dynamics under anesthesia via infusions, tilting, and inflations.[1] These results helped illuminate the underlying relationships governing the behavior of these biofluid compartments in a physiologic state. Furthermore, they are supporting the derivation of a novel quantitative model linking these compartments in a single unified system. The physiologic chronic phase serves to confirm the relationships derived during the physiologic acute with awake sheep in normal conditions, utilizing an in-house coded computer vision algorithm to estimate pose and perform statistical analysis on sheep in different targeted positions (Fig. 1), selected based on the influence they are suspected to have on physiologic dynamics.

Fig. 1. Example output using our custom in-house computer vision algorithm showing the sheep's pose in a chair (top) and kneeling below a bridge (bottom). Simultaneously acquired telemetric pressure data is used to perform statistical analysis on each position.

The pathologic acute phase elucidates comparative pathologic phenomena to the acute physiologic. To do this, a novel normal pressure hydrocephalus ovine model is being developed. Taking inspiration from Di Rocco[3], an actuation device is being developed to increase the intracranial pulse pressure without increasing the mean. This has been proven to work in pilot and we are moving forward with further trials to acquire comparative pathologic data.

This work investigates the underlying physiologic relationships governing the interconnectivity between the craniospinal, arterial, venous, and abdominal compartments. These relationships build the mathematical foundation with which novel hydrocephalus treatments can be designed and tested, improving the lives of hydrocephalus patients worldwide.

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Anthony Podgoršak

About the Presenter: Anthony Podgoršak is a PhD Candidate at the Product Development Group Zurich, ETH Zurich. Building off of his experience in large-scale interdisciplinary studies at the University of Toronto, he joined the Hydrocephalus Project in 2020 under the tutelage of Dr. Marianne Schmid Daners. Working within the field of hydrocephalus pathophysiology, his work uncovers physiologic dependencies and derives novel quantitative models that describe the craniospinal and adjacent compartments

SESSION H, FRIDAY, JUNE 17TH, 15:20 – 15:45

LEARNING THROUGH OBSERVATION IN SCIENCE: A NEUROSURGEON'S PERSPECTIVE

Harold L. Rekate MD
Professor Emeritus of Neurosurgery, Hofstra Northwell School of Medicine
Long Island, NY USA

Abstract. The intent of this presentation is to emphasize the importance of unexpected outcomes in science in general and neurosurgery in particular. The process of learning through observation is discussed based on the literature of philosophy of science and on concepts from that of education. It is essential when dealing with what philosophers of science call "anomalies" there must be a plan to deal with unexpected outcomes of patient care or scientific experiments. With a brief discussion of the history of paradigm shifts in science and personal vignettes of anomalies in my practice we are able to create an algorithm to maximize the value of new thoughts.

Dealing with anomalies requires the commitment to two distinct processes

1. Carefully focus on what has been observed without commitment to causation. Think it through and somehow store these aspects either in your mind or in a file. This does not over time.

2. Develop a theory or theories of causation. This aspect requires one or more process such as literature review, discussions with experts and creation of experiments. This part is critical and often takes time (sometimes decades). May need new devices or new thoughts.

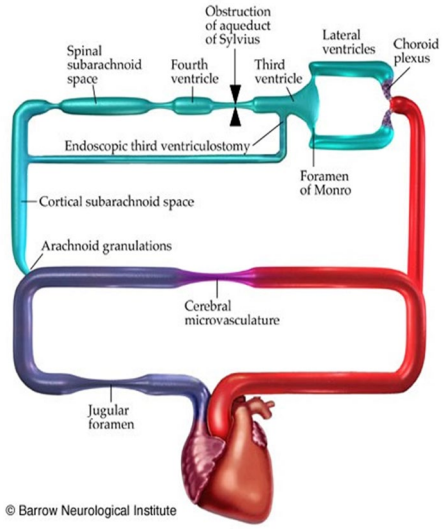

Fig. 1. Diagram of the CSF system as a circuit related to the anomalies to be discussed

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Harold Rekate

About the Presenter: Trained at Case Western Reserve Un. Cleveland, Ohio, Was chief of Pediatric Neurosurgery 1978-84, Adjunct Professor of Systems and design engineering Case Institute 1982-1990, Chief on Pediatric neurosurgery the Barrow Neurologic Institute Phoenix Arizona (1985-2010), Co-founder of the international Hydrocephalus Imaging working group (IHIWG.org). Past president of the International Society of Pediatric Neurosurgery (2000). Past President of the American Society for Pediatric Neurosurgeons 2000-2002.

CSF FLOW VOLUME IS REDUCED IN PEDIATRIC SUBJECTS WITH CHIARI BUT RETURNS TO NORMAL VALUES WITH DECOMPRESSION SURGERY

Bliss A. Uribe[1], Joshua Chern[2], John N Oshinski[1]

[1] Radiology & Imaging Science and Biomedical Engineering, Emory University, Atlanta, GA USA
[2] Neurological Surgery, Emory University, Atlanta, GA USA

Abstract. The decision to perform sub-occipital decompression surgery on pediatric patients with Type I Chiari malformation (CM-I) is highly dependent on qualitative factors such as clinical signs and reported symptoms. Hydrodynamic parameters describing CSF flow have been suggested as a quantitative marker for the impact of CM-I on CSF flow that may be altered with surgery. Although some studies have been done in Adult populations, much less is known about CSF flow in the pediatric population. In this study, we measured CSF flow with Phase Contrast Magnetic Resonance (PCMR) at the foramen magnum and C6 in pediatric CM-I patients pre- and post-surgery and in age-matched controls. *We hypothesized that cerebrospinal fluid (CSF) forward flow volumes at the foramen magnum and C6 would be different in pre-surgical CMI patients than in control patients, and that the flow volume would change post-surgery.*

10 CM-I pediatric patients (10 +/- 3.5 years of age, 4 M, 6 F) from an outpatient pediatric neurosurgery clinic underwent MR imaging pre- and post-depression surgery as part of normal clinical care. An additional 8 volunteers (7.8 +/- 5.4 years of age, 3 M, 5 F), who underwent MRIs for non-specific headache symptoms, were determined to be normal in structure and function by a neuro-radiologist and were used as control subjects. ECG gated 2D phase-contrast magnetic resonance (PCMR) scans with a spatial resolution of 1.15 mm x 1.15 mm x 5mm and 25 images per cardiac cycle were acquired in the transverse orientation at the foramen magnum (FM) and at C6. The software Segment™ was used to analyze and determine CSF flow as a function of time in the cardiac cycle at the FM and C6 points. The CSF flow parameter examined was forward flow volumes (ml), represented by the blue areas in ***Figure 1***.

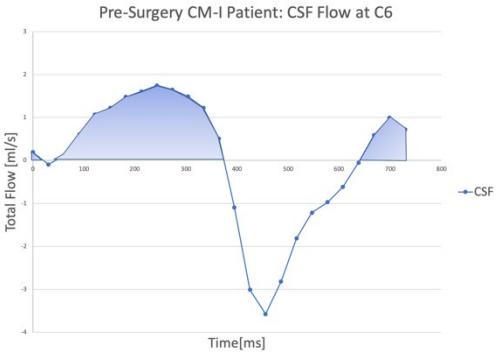

Figure 1. Pre-Surgical CM-I Patient's CSF Flow as a function of time throughout the cardiac cycle.

The mean forward volumes in the pre-surgical CM-I patients were lower than the control subjects, 0.46+/- 0.20 ml versus 0.57 +/- 0.12, $p<0.05$. The forward volumes were not significantly different in post-surgical patients CM-I compared to controls, 0.61+/- 0.23 ml versus 0.57 +/- 0.12, $p>0.05$. The pre-surgical forward volumes were significantly less than the post-surgical volumes at both the FM and C6 ($p=0.046$ and $p=0.012$, respectively for the two locations), ***Figure 2***.

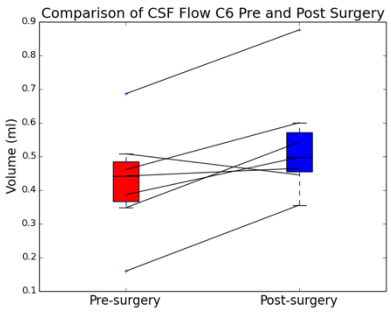

Figure 2. Box and Whisker Plot for CSF Forward Volume pre-surgery and post-surgery CM-I patients.

Pediatric control subjects had higher CSF forward flow volume than CM-I patients, and sub-occipital decompression surgery increased CSF flow volume values to values equal to normal control subjects.

Bliss Uribe

About the Presenter: Bliss Uribe graduated from the Georgia Institute of Technology in December 2021 with a Bachelor's of Science in Biomedical Engineering. She joined the Oshinski Lab in January 2022 and will continue to work on Chiari projects until she begins medical school this upcoming fall. Bliss hopes to continue working on clinical research during school and in her future career as a physician.

THE PATHS AND DRIFT OF PERIVASCULAR FLUID PARTICLES INDUCED BY ASYMMETRIC VESSEL WALL TRAVELING WAVES

Julian A. Rey[1], Sivaramakrishnan Balachandar[1], Malisa Sarntinoranont[1]

[1] Department of Mechanical and Aerospace Engineering, University of Florida, Gainesville, Florida, USA

Abstract. Rapid uptake of imaging tracers from the subarachnoid space into the perivascular spaces surrounding surface arteries and penetrating arterioles has been observed repeatedly in rodents [1]. While the inflow of cerebrospinal fluid into arterial perivascular spaces is a key component of the glymphatic system, the mechanism driving this flow is poorly understood. A leading theory is that traveling arterial wall waves, originating at the heart, pump fluid through perivascular spaces by peristalsis. While the notion of peristaltic pumping in perivascular spaces has been challenged by previous computational modeling results [2][3], there is a need to consider the trajectory of fluid particles throughout the perivascular domain because mean volumetric flow, often used to evaluate peristalsis as a driver of perivascular flow, averages out radial variation in net fluid transport. The field would also benefit from isolating the effect arterial wall wave asymmetry has on perivascular flow.

A fluid mechanical model of perivascular flow produced by a train of arterial wall waves was developed to predict fluid particle paths and drift throughout the perivascular space for both sinusoidal and asymmetric traveling waves. Due to the small radial displacement of the arterial wall relative to the perivascular width, the arterial wave was modeled as a traveling, periodic blowing profile along the perivascular inner boundary. Because viscous forces dominate the flow, the flow produced by the asymmetric, physiological wall wave was derived from the superposition of flows produced by the asymmetric wave's sinusoidal Fourier components.

The perivascular fluid velocity field was axially periodic and traveled at the arterial wave speed in the pulse propagation direction. The peak axial fluid velocity was three orders of magnitude larger than the peak radial fluid velocity, resulting in highly oblique particle trajectories with increasing eccentricity with distance from the inner perivascular boundary. Fluid particle oscillations and drift had a roughly parabolic profile with the greatest axial excursion (~200 μm) and anterograde drift (~20 μm/s) skewed slightly towards the inner wall. Pulse wave asymmetry increased the peak axial drift to ~25 μm/s (Fig. 1). While the drift profile is farily consistent with in vivo observations of microsphere motion in the perivascular space, the axial excursion is larger than observed and may be a consequence of a difference between microsphere and fluid motion or the assumption of a fixed perivascular outer boundary. The arterial traveling wave also produced retrograde fluid particle drift near the outer perivascular boundary, a feature of peristalitc flows identifiable only by considering fluid particle paths and which should enter the discussion of peristalsis in perivascular spaces.

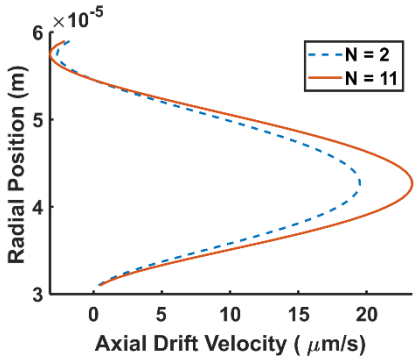

Fig. 1. Axial drift of fluid particles for a sinusoidal (N=2) and asymmetric (N=11) arterial wall wave.

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2. Asgari et al. (2016). Glymphatic solute transport does not require bulk flow. Scientific Reports 6:38635.
3. Kederasetti et al. (2020). Arterial pulsations drive oscillatory flow of CSF but not directional pumping. Scientific Reports 10:10102.

Julian A. Rey

About the Presenter: Julian A. Rey is a doctoral candidate in the Department of Mechanical and Aerospace Engineering at the University of Florida that specializes in image-guided modeling of mechanical phenomena in the brain related to brain cancer, neurodegenerative diseases, and drug delivery.

TRANSFER FUNCTION ANALYSIS OF ARTERIAL AND CEREBROSPINAL SPACES DURING TILTING IN AN ACUTE OVINE IN-VIVO TRIAL

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Abstract. While there have been decades of research dedicated to understanding CSF dynamics within the context of Hydrocephalus, little is known about the underlying quantitative physiology dictating the interactions between the arterial and CSF craniospinal spaces. We are limited in capacity to design more sophisticated treatment methods and derive more comprehensive numerical models without first ameliorating this knowledge gap.

An ovine *in-vivo* trial (N=6) was performed to quantify interactions between the carotid arterial, intracranial, and intrathecal pressures (cABP, ICP, ITP) in anesthetized sheep under mechanical ventilation during postural changes. Tilts were performed on a surgical tilt-table between -13° and 13°, as dictated by hardware restrictions. Neutral body position was classified as 0°, full head-over-body (HoB) at 13°, and full body-over-head (BoH) at -13°. Time series waveforms are converted into the frequency domain using fast Fourier transforms (FFT) and transfer functions (TF) are defined as output (ICP, ITP) over input (cABP) in the Fourier space. Transfer functions are calculated for neutral, HoB, and BoH positions to acquire a comprehensive look at how posture influences waveform propagation. Temporal offsets are calculated via cross-correlation.

In our study, the mean heart rate (HR) and respiratory rate (RR) at baseline were analysed to be 1.55 and 0.31 Hz, respectively. From baseline to 13° and -13°, the HR changed -2.2 and 2.0%, respectively. cABP-ICP and cABP-ITP TFs displayed bandpass and lowpass filter characteristics, seemingly as dictated by the cardiac harmonics. Cardiac-driven propagation times were analyzed as ABP-to-ICP: 76±41-62±36, ABP-to-ITP: 138±52-138±38, and ICP-to-ITP: 62±66-66±39 ms from -13° to 13°.

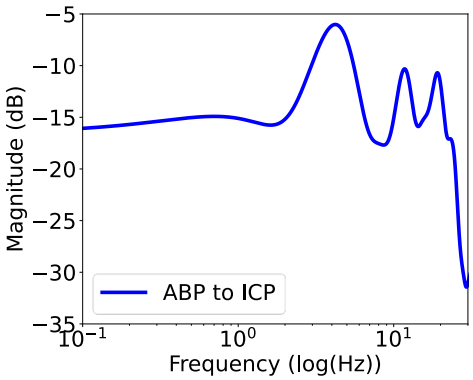

Fig. 1. Derived transfer function between the carotid arterial and intracranial pressures at 0° of tilt. An initial local min occurs at 1.68 Hz followed by the absolute max at 4.24 Hz suggesting bandpass filter behaviour. Two further local maxima occur at 11.61 and 19.59 Hz, followed by attenuation of all higher frequencies.

It is long established that there exists an autonomic modulation of HR during changes in posture, indicating a healthy carotid sinus reflex (1). Interestingly, even under mechanical ventilation, there existed RR variation between BoH, HoB, and baseline, perhaps in response to the increased HR. cABP-ICP and cABP-ITP TFs shared similar nature across all sheep investigated, only the location of the extrema and bandwidth of the initial bandpass behaviour varied, highlighting their hydraulic connection. Propagation times between the three unique spaces displayed no discernable pattern between them, implying different gravitational influences on each compartment between -13° and 13°.

1. MacWilliam, JA (1933). POSTURAL EFFECTS ON HEART-RATE AND BLOOD-PRESSURE. Quarterly Journal of Experimental Physiology 23 (1): 1-33.

Anthony Podgoršak

About the Presenter: Anthony Podgoršak is a PhD Candidate at the Product Development Group Zurich, ETH Zurich. Building off of his experience in large-scale interdisciplinary studies at the University of Toronto, he joined the Hydrocephalus Project in 2020 under the tutelage of Dr. Marianne Schmid Daners. Working within the field of hydrocephalus pathophysiology, his work uncovers physiologic dependencies and derives novel quantitative models that describe the craniospinal and adjacent compartments.

MODELING INTRACRANIAL PRESSURE IN THE SUBARACHNOID SPACE AND LATERAL VENTRICLE OF ANESTHETIZED RATS

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Abstract. There is growing evidence that intracranial pressure (ICP) plays a role in glaucoma since the lamina cribrosa of the optic nerve head is exposed to intraocular pressure (IOP) on one side and ICP on the other. The purpose of this study is to understand CSF dynamics by modeling ICP responses to fluid infusion in different cranial compartments. Experiments were done on anesthetized adult Brown-Norway rats. Anesthesia was induced with an intramuscular bolus of ketamine-xylazine and maintained by intravenous infusion of ketamine. The animal was rested on a heating pad that held body temperature at physiological levels and heart rate was continually monitored with ECG electrodes. The head was affixed in a stereotaxic apparatus and the skull was surgically exposed. ICP in the subarachnoid and ventricular compartments was concurrently recorded via a vented screw in the skull and 25-gauge needle inserted into a cerebral ventricle, respectively. IOP was simultaneously recorded as well via a 33-gauge needle in the anterior chamber of one eye. In some experiments, pressure in one of the cerebral compartments was elevated by varying the height of a saline reservoir connected via a three-way stopcock to the vented screw or 25-gauge needle. In other experiments, saline was infused at different rates into one of the cerebral compartments with a programmable syringe pump. The resistance of system tubing and cerebral compartments was estimated from steady-state pressure-flow data. The compliance of system tubing and cerebral compartments was estimated from the instantaneous pressure change to fluid bolus injections of increasing volume in a dead rat. Elevating vICP 5 to 15 mmHg above baseline increased sICP with exponential response dynamics by a lower amount, as shown in Fig. 1A. Whereas, elevating sICP had much less impact on vICP and response dynamics were much slower. To understand these observations a fluid mechanical model, illustrated in Fig. 1B, was created to simulate CSF pressure and flow behavior in the two compartments and model predictions were compared with experimental results for constant flow and constant pressure perturbations. System tubing resistance and compliance were 0.014 mmHg·min/µL and 0.098 µL/mmHg, respectively. The resistance and compliance of the ventricle compartment were estimated to be 0.098 mmHg·min/µL and 0.414 µL/mmHg, which was much less than the resistance (0.695 mmHg·min/µL) and hypothesized compliance (5 µL/mmHg) of the subarachnoid compartment (n = 2). Average error of the vICP and sICP prediction was <2% and <9%, respectively. We conclude that ICP of rats is nearly identical in the subarachnoid space and lateral ventricle at baseline but that ICP dynamics differ between the compartments, resulting in a delayed sICP response to vICP perturbations. The amplitude and dynamics of ICP changes can be described by a two-compartment model to a first approximation.

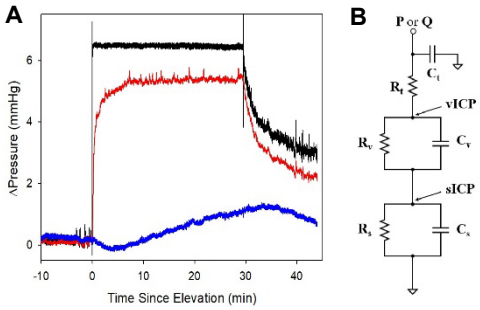

Fig. 1. **(A)** Concurrent recording of vICP (black), sICP (red) and IOP (blue) in one animal showing an IOP response to vICP elevation of about 6.5 mmHg **(B)** Simplified electrical model of fluid moving from an external pressure (P) or current (Q) source through tubing with resistance and compliance R_t and C_t, respectively, into a lateral ventricle (vICP, R_v, C_v) and then eventually into the subarachnoid space (sICP, R_s, C_s) to be cleared.

Cesar Hernandez Isidro

About the Presenter: Cesar Hernandez Isidro is a second year Biomedical Engineering Ph.D. student working in the Ocular Neuroscience and Neuroengineering Lab at the University of South Florida. His research is primarily focused on the interplay between intracranial pressure and intraocular pressure in healthy and glaucomatous eyes.