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Poster Presentations

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Increase in cerebral blood flow on brain magnetic resonance angiogram following correction of cervical lordosis

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Abstract

Background: Loss of cervical lordosis is associated with decreased vertebral artery hemodynamics. Vertebral arteries merge forming the basilar artery which continues to the circle of Willis and cerebral arteries. A close anatomical relationship exists between the cervical spine, vertebral arteries, and cerebral vasculature.

Aim: Evaluate cerebral blood flow changes on brain MRA in patients with loss of cervical lordosis prior to and following correction of cervical lordosis.

Method: This study is a retrospective consecutive case series. Cervical lordosis of seven patients (five females, two males, 28 to 58 years) was measured on lateral cervical radiographs ranging from −13.1 to 19.0 degrees (ideal is −42.0 degrees). Brain MRAs were analyzed for pixel intensities representing blood flow. Pixel intensity of the cerebral vasculature was quantified, and percent change determined.

A student's t-test established significance of percent change in cerebral blood flow between pre- and post-cervical lordosis adjustment images. Regression analysis was performed. An a priori analysis determined correlation between cervical lordosis and change in MRA pixel intensity. The statistician was blinded to cervical lordosis.

Results/Conclusions: Pixel intensity increased 23.0 to 225.9% and a student's t-test determined the increase was significant ($p < 0.001$). Regression analysis of change in pixel intensity versus cervical lordosis showed that as deviation from a normal cervical lordosis increases, percent change in pixel intensity on MRA decreases.

These results indicate that correction of cervical lordosis may be associated with immediate increase in cerebral blood flow. Further studies are needed to confirm these findings and understand clinical implications.

Table 1. Cervical Lordosis and Cerebral Blood Flow Quantifications of Participants for Pre and Post Cervical Lordosis Adjustment MRA.

Participant	Normal ARA C2–C7 (°)	ARA C2-C7 (°)	Deviation from ideal ARA C2–C7 (°)	Pre-Adjustment MRA area over threshold (in^2)	Post-Adjustment MRA area over threshold (in^2)	Pre-adjustment MRA total pixel intensity	Post-adjustment MRA total pixel intensity	Percent change in total pixel intensity (%)	Pre-adjustment MRA threshold
1	−42.0	19.0	61	0.444	0.525	453094	557461	23.0	76
2	−42.0	6.7	48.7	0.257	0.311	190537	240016	26.0	60
3	−42.0	3.7	45.7	0.104	0.273	84668	249567	194.8	70
4	−42.0	3.0	45	0.304	0.427	300480	444834	48.0	79
5	−42.0	−11.8	30.2	0.190	0.256	170810	256071	49.9	70
6	−42.0	−13.1	28.9	0.333	0.655	386883	841061	117.4	90
7	−42.0	−20.4	21.6	0.235	0.607	176260	574491	225.9	65
Mean	−42.0	−1.8	40.2	1.721	2.815	251819	451929	97.9	73

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In vitro identification of mannose binding lectin inhibitors as neuroprotective strategy for ischemic brain injury

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Abstract

Background: Experimental evidence indicates that circulating mannose binding lectin (MBL) binds the sugar moieties exposed on endothelial cell membranes after brain ischemia, eventually driving pathogenic thromboinflammatory cascades. As such MBL is a putative pharmacological target.

Aim: Identification of nanoparticle-based MBL inhibitors by novel in vitro approaches.

Methods: We set up a novel Surface Plasmon Resonance (SPR) based assay to screen MBL inhibitors. The selected inhibitor was tested for toxicity and efficacy on a cell model of ischemia-induced endothelial damage.

Results/Conclusions: The new SPR-based-assay showed that recombinant MBL (rhMBL) bound the sugar-coated SPR chips with high affinity (KD 2.3 ± 0.3 nM). This binding was reduced if rhMBL was pre-incubated with monovalent mannose (IC50 = 5 mM), with a nine mannose-residues carrying glycan (IC50 = 0.33 mg/mL) and more effectively with mannose-coated gold nanoparticles (man-GNP, IC50 = 1.1 μg/mL). The method could also measure the inhibition of serum endogenous MBL. Man-GNP ability to inhibit MBL's toxic functions were analyzed ihBMECs subjected to hypoxia and re-oxygenation in presence of serum MBL. In vitro ischemia induced structural damage and inflammation (increased IL-1α, MMP-2 and ICAM-1 gene expression). These effects were not ameliorated by administering 40 μg/mL of man-GNPs, possibly due to excessive dosing of GNP. Next smaller doses, namely 5 and 20 μg/mL, were tested with the latter showing reduction of MMP2 overexpression to a similar extent than when MBL-deprived serum was applied. In conclusion, we successfully developed a SPR tool for screening MBL inhibitors and identified a promising dosing before in vivo studies.

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The effects of anemia and microvascular hemodynamics on cerebral tissue PO2 in sickle cell disease

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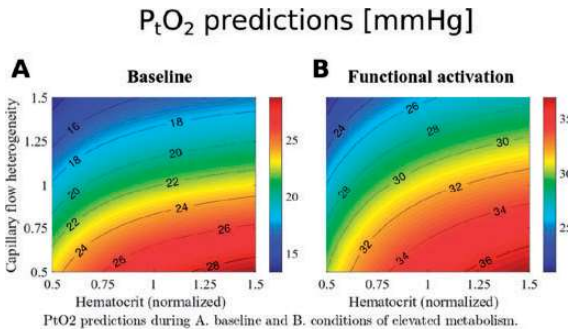
Abstract

Background: Sickle cell disease (SCD) is one of the most common genetic disorder observed in newborns.[1] SCD is due to a mutation in the beta-globin gene, resulting in distorted erythrocytes, altered oxygen–hemoglobin dissociation curve (ODC) and anemia.[1] SCD patients show low arterial blood oxygen content, altered blood rheology and presumably elevated capillary flow heterogeneity (CFH),[2] paralleled by endothelial damage and chronic inflammation.[3]

Aim: Here, we examine the extent to which altered microvascular hemodynamics and reduced hematocrit as observed in SCD affects cerebral tissue oxygen tension (PtO2). In particular, we address the transit-time effects that arise as functional and compensatory (to low blood oxygen content) hyperemia shorten the time available for capillary blood-tissue oxygen exchange.

Method: We developed a four-compartment biophysical model to infer PtO_2 from erythrocytes capillary transit-time characteristics. The model takes into account microvascular parameters that are altered in SCD (e.g., blood flow, hematocrit, CFH, ODC). We performed a sensitivity analysis to quantify the importance of these parameters on PtO_2.

Results/Conclusions: Our model predicts that altered microvascular hemodynamics in SCD lead to significantly reduced PtO_2. The influence of the model parameters is predicted to depend on the physiological condition (see Figure 1). In future work, our model will be applied to experimental data set to examine whether estimated PtO_2 can predict symptoms severity associated with SCD, such as cognitive impairment or risk of ischemic injury.[1,4]



PtO2 predictions during A. baseline and B. conditions of elevated metabolism.

References

1. Ashley-Koch et al., *AmJEpidemiol* 2000).
2. Vu et al. *Am J Hematol* (2021).
3. Conran and Belcher. *Clin Hemorheol Microcirc* (2018).
4. Amendah et al. *Am J PrevMed* (2010).

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Evaluating the mechanism behind hyperhomocysteinemia induced blood brain barrier breakdown

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Abstract

Background: Vascular contributions to cognitive impairment and dementia (VCID) is one of the leading causes of dementia. High levels of plasma homocysteine or hyperhomocysteinemia has been characterized as a risk factor for VCID however, the mechanism underlying this connection remains elusive.

Aim: I hypothesize that hyperhomocysteinemia initiates a pro-inflammatory cascade that increases the activity of matrix metalloproteinase 9 (MMP9) leading to blood brain barrier dysfunction and the progression toward VCID pathology.

Method: C57BL6 WT and MMP9 knock out mice were placed on a control diet or a diet deficient in folate, vitamins B6 and B12 and enriched in methionine to induce hyperhomocysteinemia for 4, 8, 12, and 16 weeks. Immunohistochemistry and gene expression analysis were used to determine neuroinflammatory changes while histology was used to identify changes in astrocytic end-feet proteins and microhaemorrhages. Both gel and *in situ* zymography were used to assess proteinase activity of MMP9 and related gelatinases. Western blots were used to investigate substrates of MMP9 including claudin, occludin and β-dystroglycan. Behaviour was assessed using rotarod, novel object recognition and spontaneous alternation testing.

Results/Conclusions: Studies are underway to examine changes in cognition, microhaemorrhages, neuroinflammation, astrocyte end-foot integrity, and activity of both MMP2 and MMP9 families. Collectively, our findings suggest that MMP9 may play an integral role in the mechanism associating homocysteine induced neuroinflammation with vascular pathogenesis leading to VCID. Continued study of the cell specificity and mechanism of MMP9 mediated vascular pathology will allow us to systematically target the various stages of disease.

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Pharmacological depletion of senescent endothelial cells improves blood-brain barrier integrity in mice with whole-brain irradiation

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