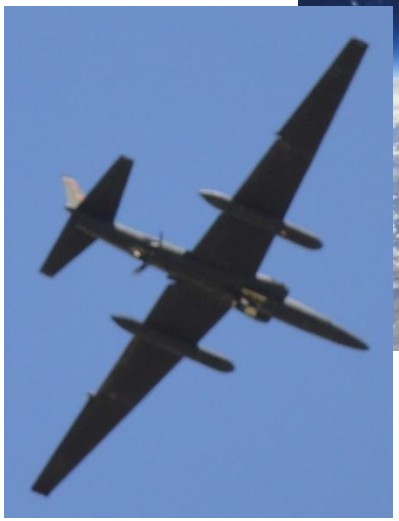
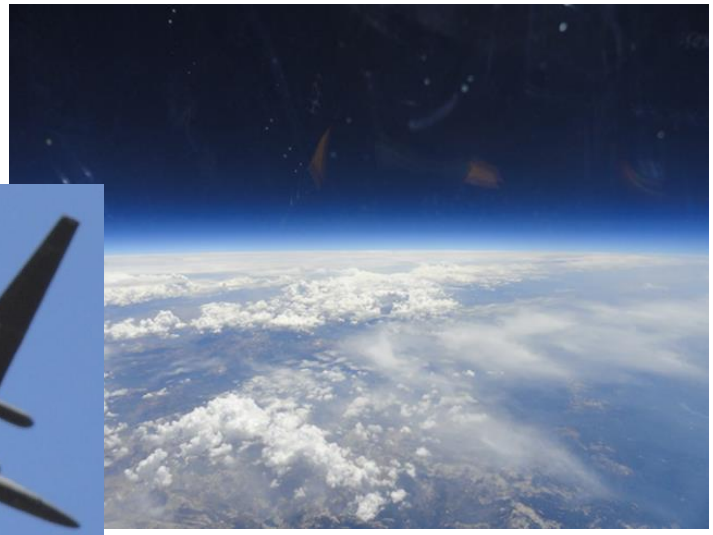
Possible Cellular Explanation for MRI Changes Following Hypobaric Exposure





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14 Sept 2017

Integrity ★ Service ★ Excellence

Disclaimer

The views expressed are those of the author and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the U.S. Government.

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What We Think We Know (Human)

- ***Recurrent exposure to nonhypoxic extreme hypobaria incites:***
  - ***Focal punctate subcortical white matter hyperintensities (WMH) on MRI***
  - ***Diffuse decrement in axonal integrity on MRI***
  - ***Acquired neurocognitive decline as measured on CBT***
  - ***Clinical neurological decompression sickness is not a prerequisite for abnormalities***
- ***Single exposure to extreme hypobaria/hypoxia (routine occupational aircrew training) incites:***
  - ***Increase in white matter followed by gray matter cerebral blood flow that persists at 72 hours post-exposure on MRI***
  - ***Consistent with increased cerebral metabolic demand***
- ***Quantitative serial MRI highly reproducible***

McGuire et al. Neurol 2013;81:729-735
McGuire et al. Ann Neurol 2014;76:719-726
McGuire et al. Neurol 2014;83:638-645
McGuire et al. Aerosp Med Hum Perform 2016;87:983-988
McGuire et al. Brain Behav 2017;e00759 (https://doi.org/10.1002/brb3.759)

Phase 2 Single Exposure MR Spectroscopy Reproducibility

- ***Reproducibility of measurement of multiple neurometabolites with MR spectroscopy (TE30) in frontal (white matter) and anterior cingulate (mixture of white and gray matter)***
  - *Glu=glutamate*
  - *tCho=choline*
  - *tNAA=n-acetylasparate*
  - *mI=myo-inositol*
  - *tCr=creatine*
  - *Glu+Gln=glutamate + glutamine*
  - *GSH=glutathione*
- ***tNAA reflects neurons***
- ***mI reflects glia***
- ***GSH reflects oxidative stress***
- ***tCr reflects energy***

- *Rating reflects # of subjs needed:*
  - *High = 1-20*
  - *Moderate = 21-40*
  - *Low > 40*

Metabolite	ICC	Rating (3%)	Rating (10%)
TE30 frontal lobes WM			
Frontal Mean Glu	0.816	N = 141(Low)	N = 14(High)
Frontal Mean tCho	0.886	N = 91(Low)	N = 9(High)
Frontal Mean tNAA	0.694	N = 51(Low)	N = 6(High)
Frontal Mean mI	0.745	N = 155(Low)	N = 15(High)
Frontal Mean tCr	0.565	N = 84(Low)	N = 9(High)
Frontal Mean Glu+Gln	0.818	N = 119(Low)	N = 12
Frontal Mean GSH	0.696	N = 281(Low)	N = 26(Mod)
TE30 AC GM			
AC Glu	0.763	N = 43(Low)	N = 5(High)
AC GSH	0.798	N = 87(Low)	N = 9(High)
AC tCho	0.879	N = 52(Low)	N = 6(High)
AC tNAA	0.787	N = 15(High)	N = 3(High)
AC mI	0.781	N = 44(Low)	N = 6(High)
AC tCr	0.667	N = 21(Mod)	N = 3(High)
AC Glu+Gln	0.765	(Low)	N = 4(High)

McGuire et al. Brain Behav 2017;e00759 (https://doi.org/10.1002/brb3.759)

Phase 2 Single Exposure MRS – Single Factor

- *In addition to ASL see difference in serial MRI measurement response to exposure by Group*
  - *Suggests some metabolites are altered by exposure*
  - *Raises possibility that response to exposure might be predicted based on baseline vlaues*

- *gam (factor ~ s(MRINum,k=3) + MRINum:Group + Group + Age*Group:MRINum + Age + Sex*Group:MRINum + Sex; AFCNOR)*
  - *Utilizing Generalized Additive Model*

Factor	Group:MRINum (p-value)
AvgGMASL	0.048
AvgWMASL	0.001
LNFLAIR	0.007
AvgFA	0.496
AvgGluFront30	0.368
AvgChoFront30	0.587
AvgNAAFront30	0.219
AvgMIFront30	0.151
AvgCrFront30	0.158
AvgGluGlnFront30	0.124
AvgGSHFront30	0.029
GluAC30	0.017
GSHAC30	0.090
ChoAC30	0.010
NAAAC30	0.023
MIACC30	0.039
CrACC30	0.008
GluGlnACC30	0.004

Phase 2 Single Exposure MRS – Correlation with ASL

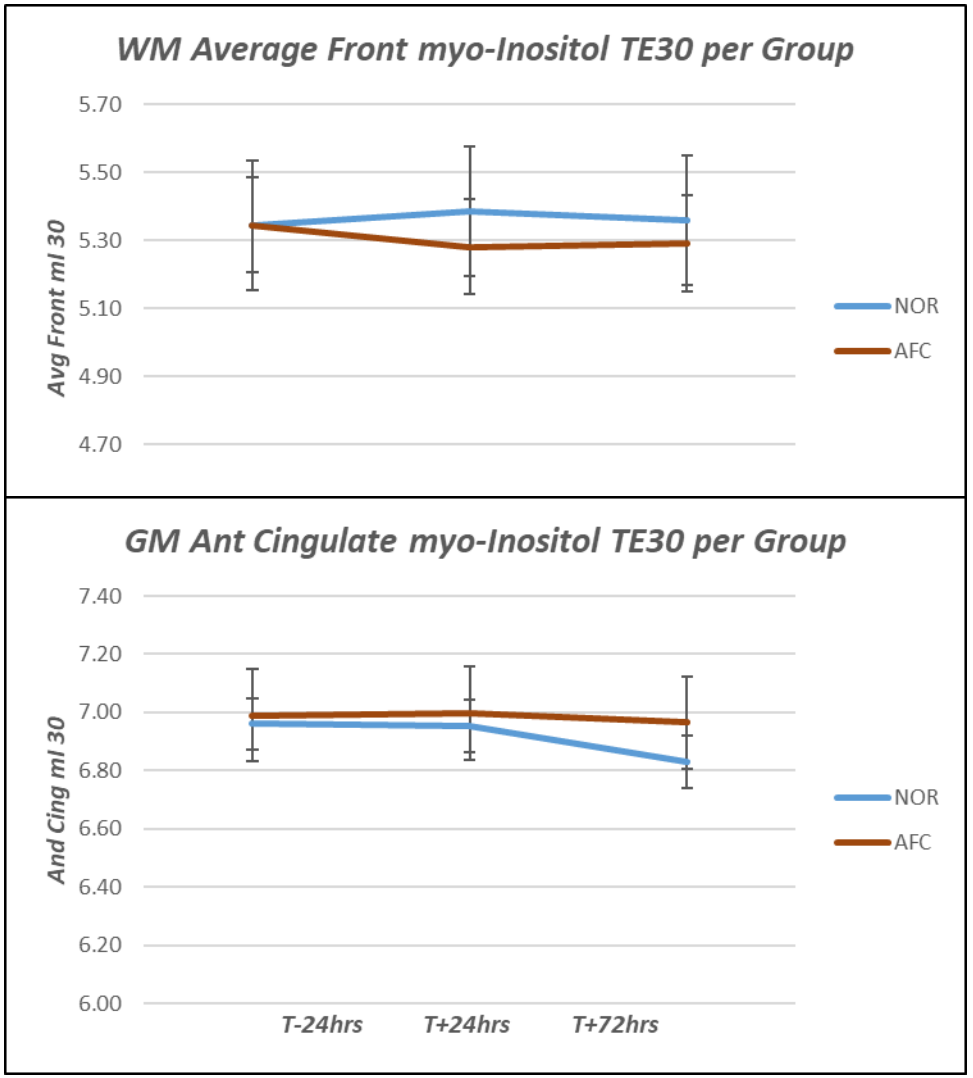
- ***Cerebral blood flow appears driven by cellular metabolite changes with MRI factor value different between groups***

- ***gam (ASL ~ s(MRINum,k=3) + factor*Group + MRINum:Group + Group + Age*Group:MRINum + Age + Sex*Group:MRINum + Sex; AFCNOR)***
  - ***Using Generalized Additive Model***

Factor	GMASL (p-value)	WMASL (p-value)
AvgGluFront30	0.058	0.004
AvgChoFront30	0.043	<0.001
AvgNAAFront30	0.028	0.001
AvgMIFront30	0.021	<0.001
AvgCrFront30	0.039	0.001
AvgGluGlnFront30	0.054	0.004
AvgGSHFront30	0.043	0.001
GluAC30	0.014	<0.001
GSHAC30	0.013	<0.001
ChoAC30	0.036	<0.001
NAAAC30	0.014	<0.001
MIACC30	0.051	0.001
CrACC30	0.021	<0.001

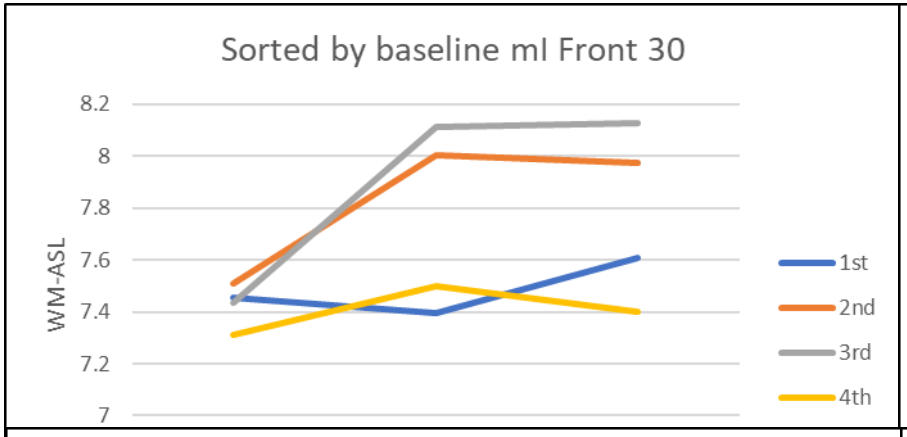
Phase 2 Single Exposure MR Spectroscopy myo-Inositol

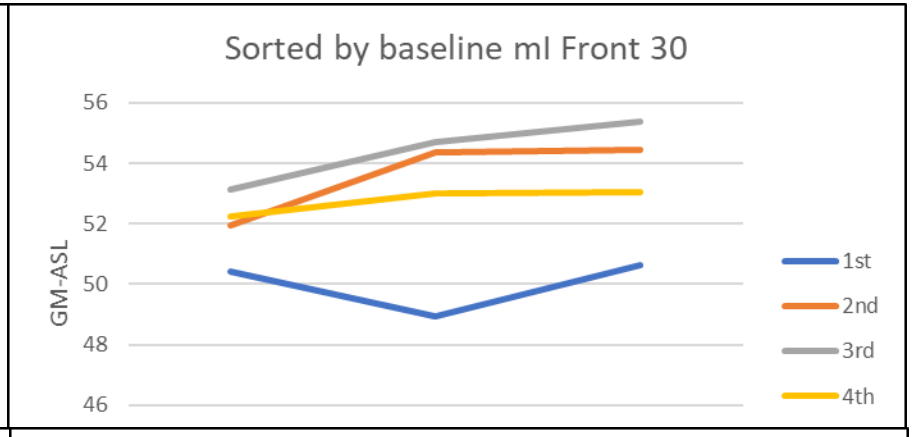
- *Difference in myo-Inositol by group after exposure*
- *Single factor analysis:*
  - *Frontal WM p=0.151*
  - *Ant Cing GM p=0.039*
- *ASL value prediction (ml) adding ml as an independent variable:*
  - *Frontal WM*
    - *WM-ASL p<0.001*
    - *GM-ASL p<0.001*
  - *ACC GM*
    - *WM-ASL p=0.790*
    - *GM-ASL p=0.153*
- *gam (ASL ~ s(MRINum,k=3) + factor*Group + MRINum:Group + Group + Age*Group:MRINum + Age + Sex*Group:MRINum + Sex; AFCNOR)*

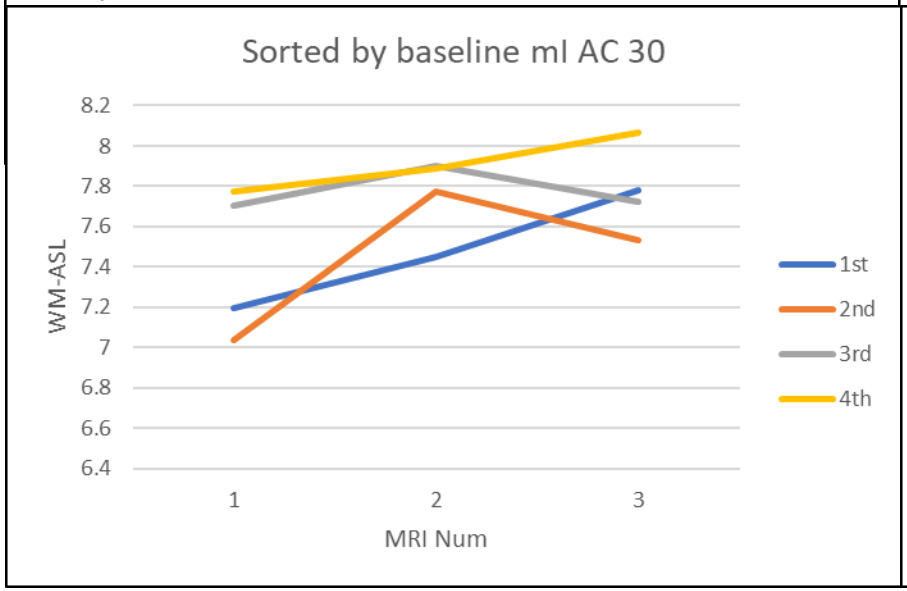


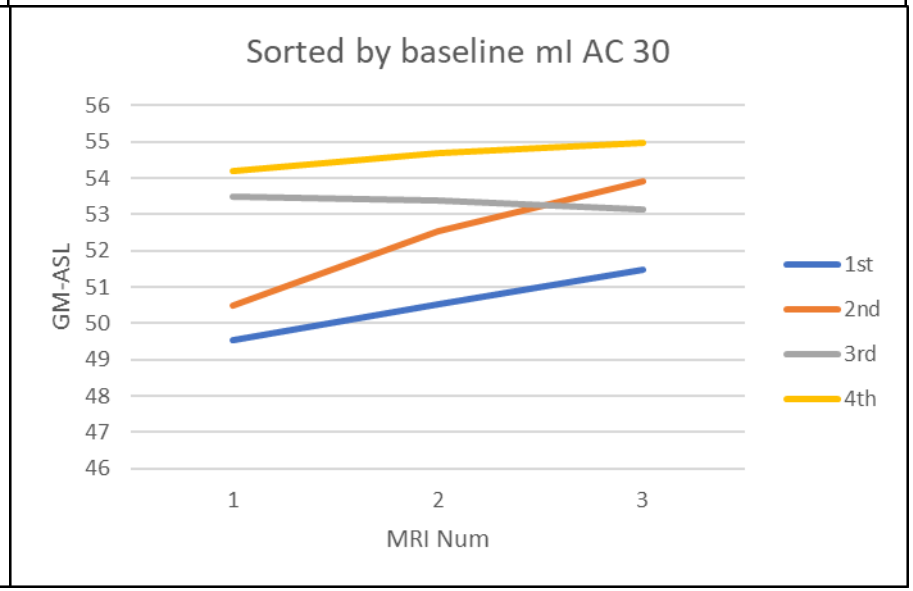
Phase 2 Single Exposure MR Spectroscopy myo-Inositol

- ***Baseline mI level suggests a difference in ASL response in AFC***



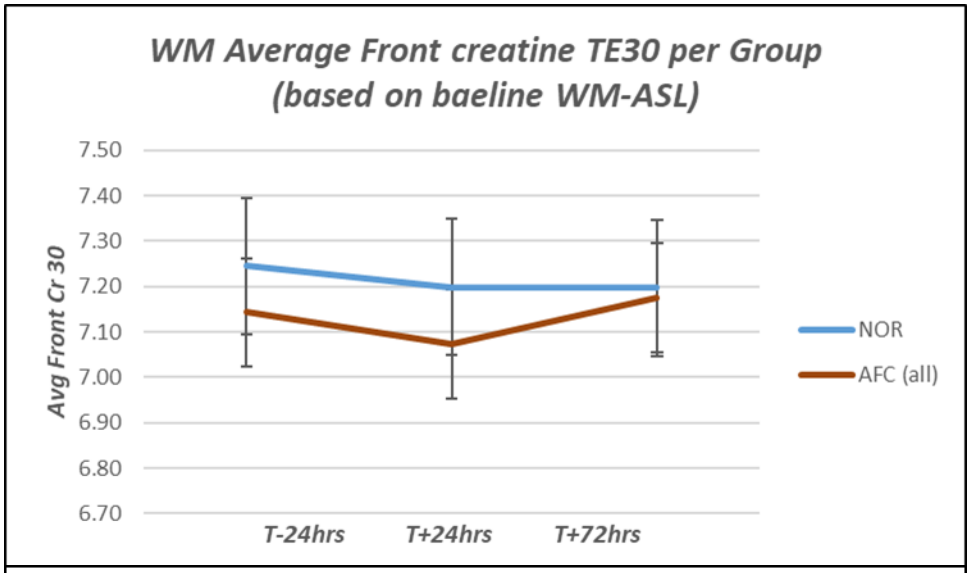


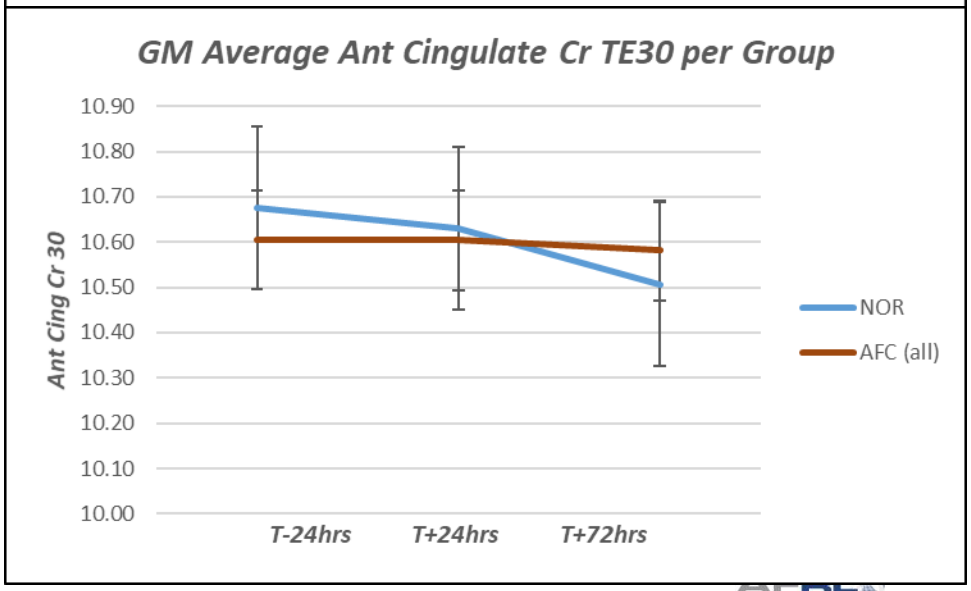




Phase 2 Single Exposure MR Spectroscopy Creatine

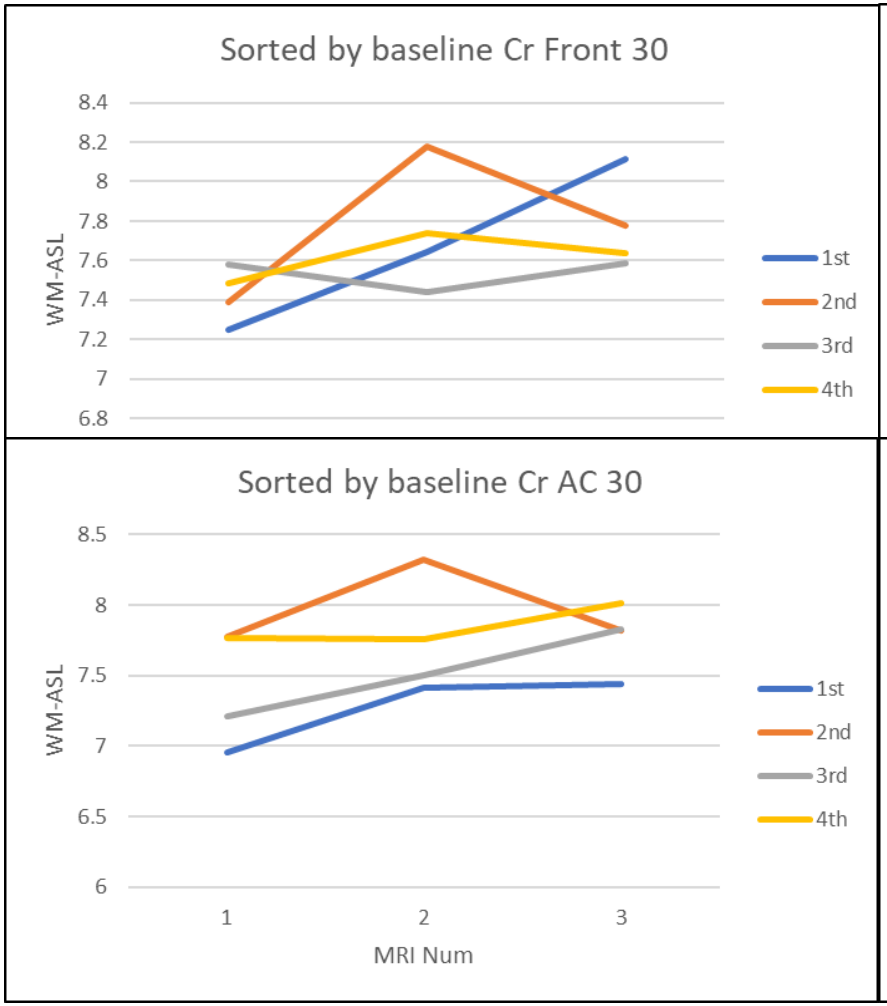
- *Difference in creatine by group after exposure*
  - *Frontal WM p=0.158*
  - *Ant Cing GM p=0.008*
- *ASL value prediction (Cr) adding Cr as an independent variable:*
  - *Cr : Group ASL prediction*
    - *Frontal WM*
      - *WM-ASL p<0.001*
      - *GM-ASL p=006*
    - *ACC GM*
      - *WM-ASL p=0.836*
      - *GM-ASL p=0.701*
- *gam (ASL ~ s(MRINum,k=3) + factor*Group + MRINum:Group + Group + Age*Group:MRINum + Age + Sex*Group:MRINum + Sex; AFCNOR)*

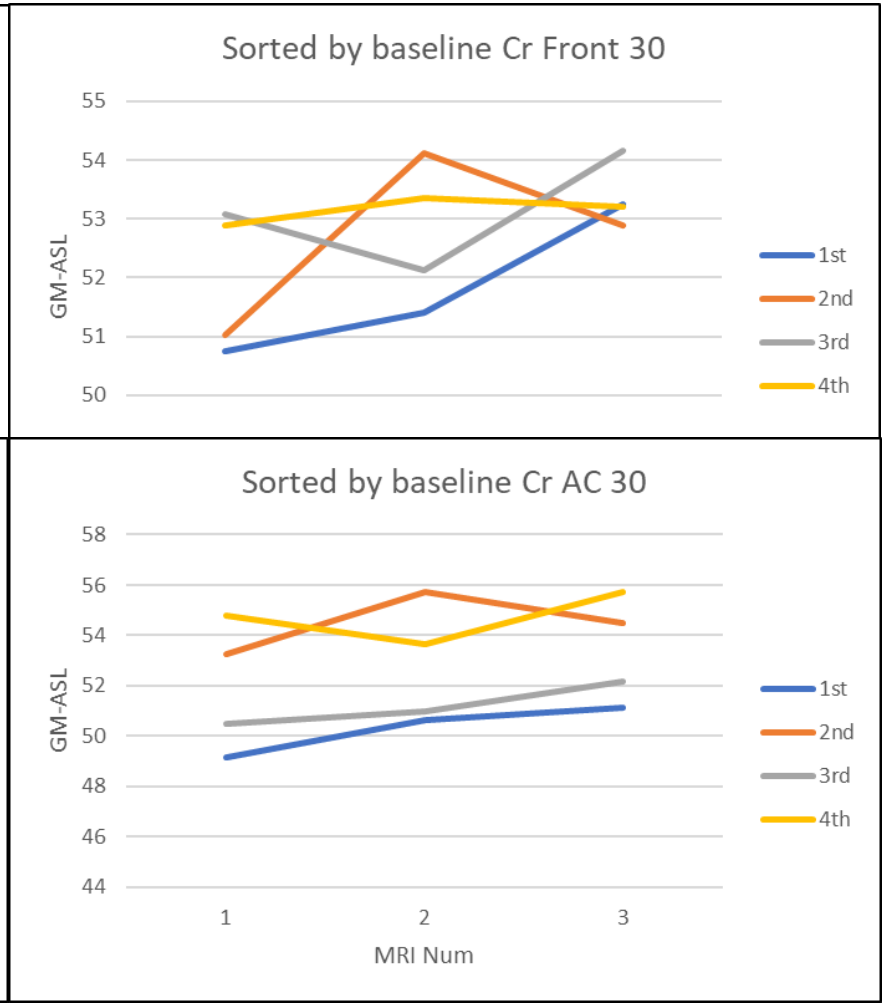




Phase 2 Single Exposure MR Spectroscopy Creatine

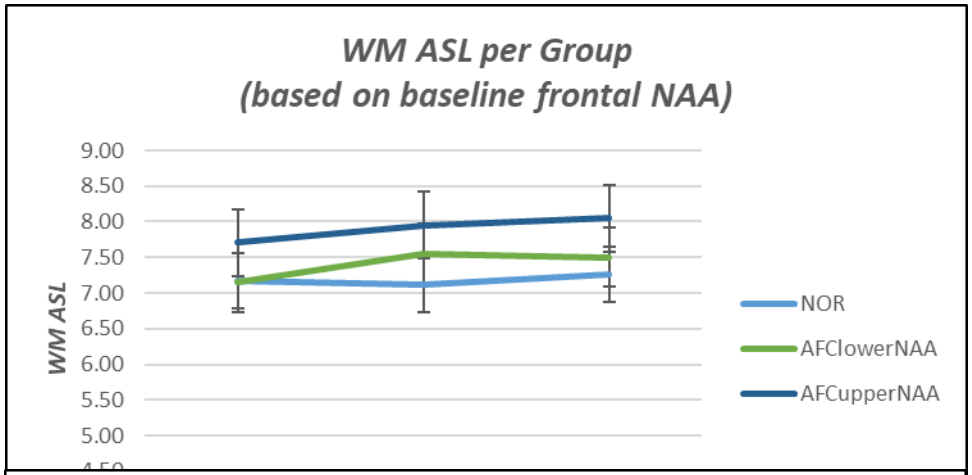
- ***Baseline Cr level suggests a difference in ASL response in AFC***

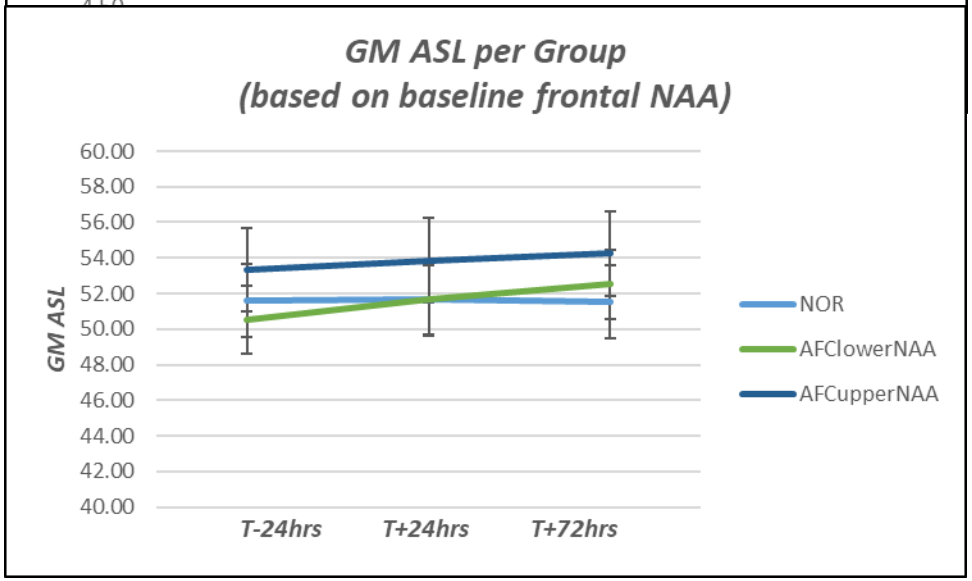




Phase 2 Single Exposure MR Spectroscopy NAA

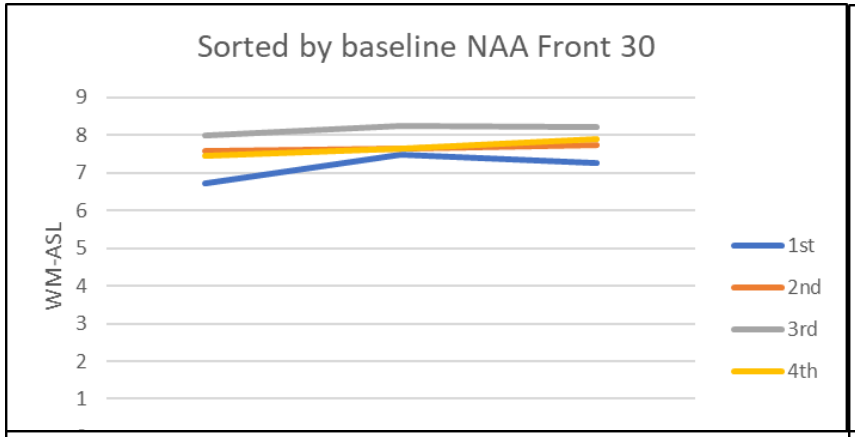
- *Difference in NAA by group after exposure*
  - *Frontal WM p=0.219*
  - *Ant Cing GM p=0.0323*
- *ASL value prediction (NAA) adding NAA as an independent variable:*
  - *NAA : Group ASL prediction*
    - *Frontal WM*
      - *WM-ASL p=0.687*
      - *GM-ASL p=0.616*
    - *ACC GM*
      - *WM-ASL p=0.274*
      - *GM-ASL p=0.132*
- *gam (ASL ~ s(MRINum,k=3) + factor*Group + MRINum:Group + Group + Age*Group:MRINum + Age + Sex*Group:MRINum + Sex; AFCNOR)*

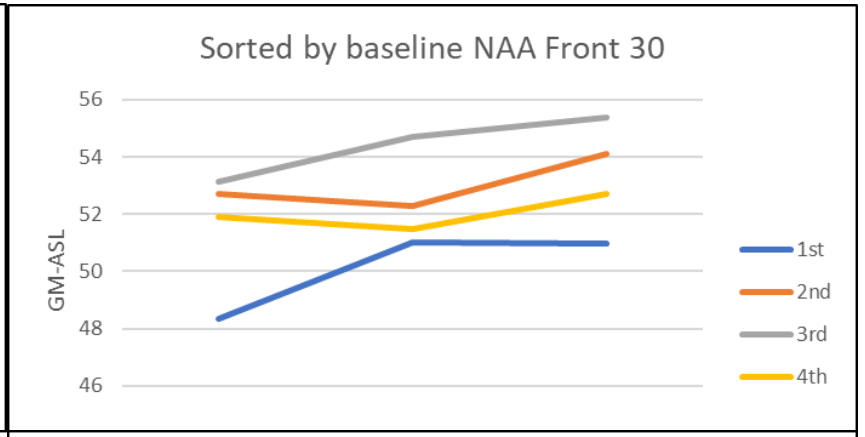


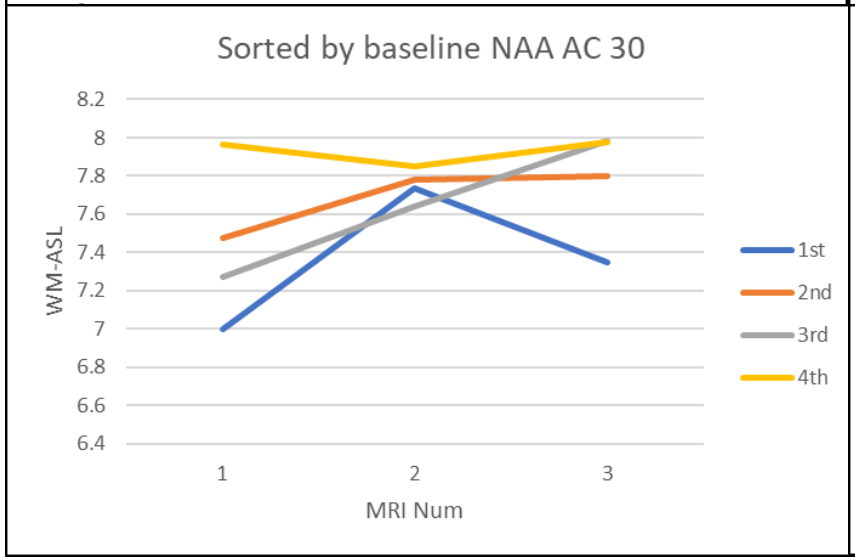


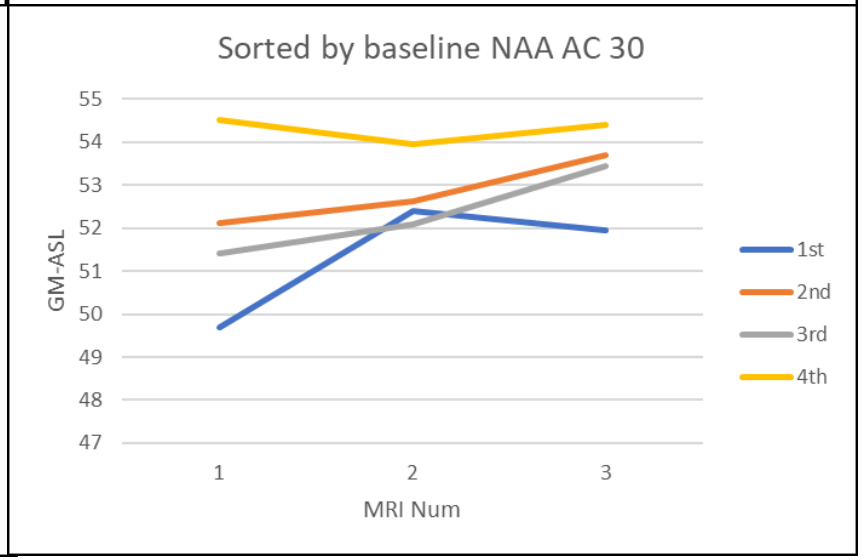
Phase 2 Single Exposure MR Spectroscopy NAA

- ***Baseline NAA level suggests a difference in ASL response in AFC***







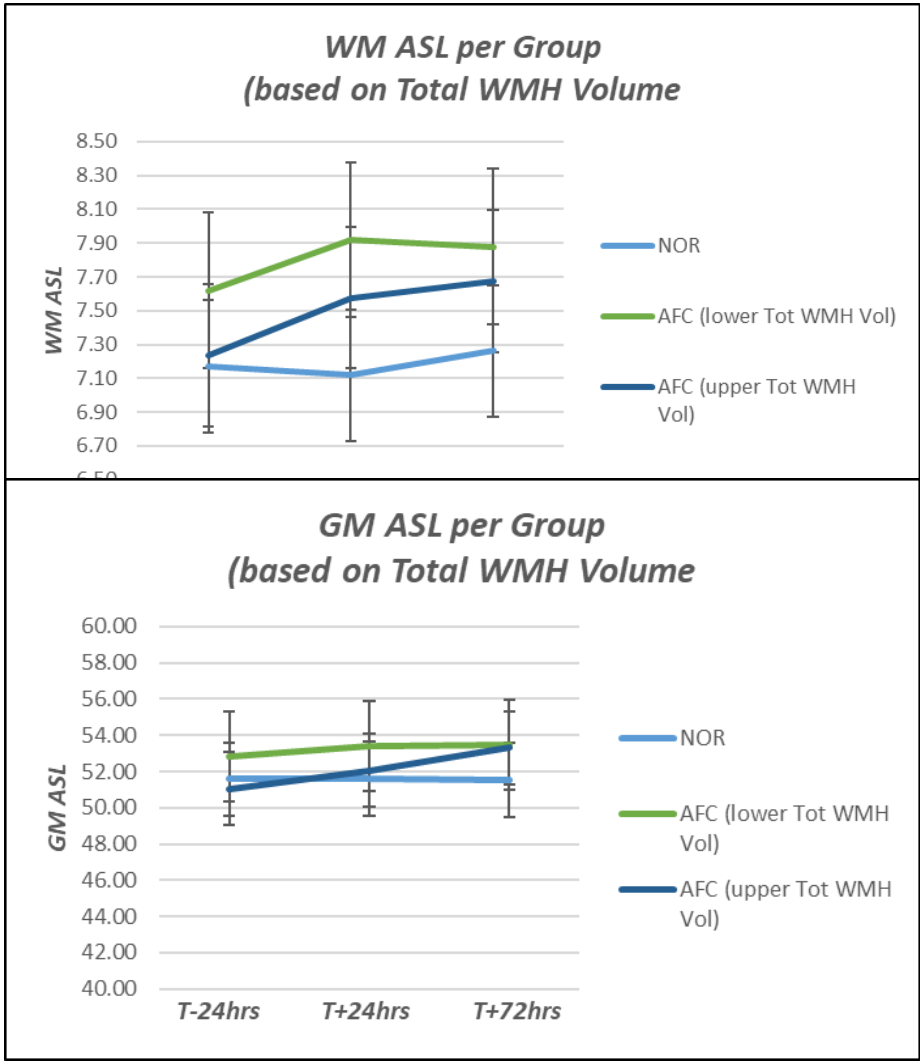


Phase 2 Single Exposure MR FLAIR Total WMH Burden

- ***Cerebral blood flow appears to be associated with the pre-existing FLAIR WMH burden***
- ***Higher WMH baseline predicts greater WM-ASL response to stress***

- ***LNFLAIR: Group***
  - ***GM ASL (p=0.628)***
  - ***WM ASL (p=0.073)***

- ***gam (ASL~s(MRINum,k=3) + factor*Group + MRINum:Group + Group + Age*Group:MRINum + Age +Sex*Group:MRINum + Sex; AFCNOR)***



What We Think This Means (Human)

- ***Single occupational exposure to a hypobaric/hypoxic environment is associated with an increase in CBF***
  - ***CBF tightly regulated by cerebral metabolic demands***
  - ***Chamber exposure to 25k feet ~ 30 minutes***
  - ***Hypoxic portion ~ 2-4 minutes historically correlating with a PaO_2Sat ~ 65-75%***
- ***The degree of ASL change appears related to baseline neurocellular metabolites***
- ***The degree of ASL change appears related to baseline Total FLAIR burden***
  - ***Suggests inherent predisposition for injury with subsequent elevated ASL***

Swine Model

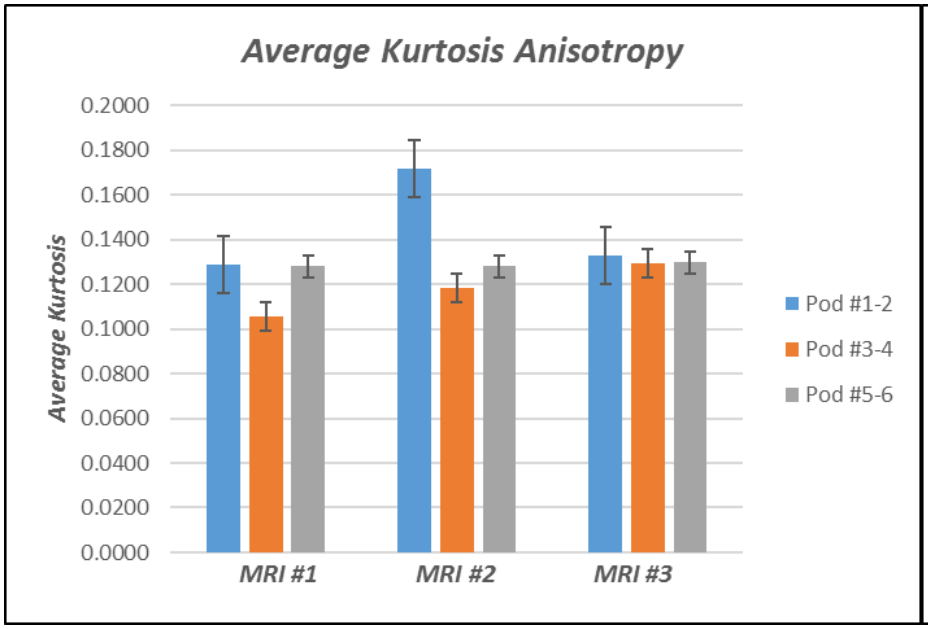
- ***Model 1 failed 2˚ to complications from anesthesia and/or DCS***
- ***Phase 2 well tolerated by swine***

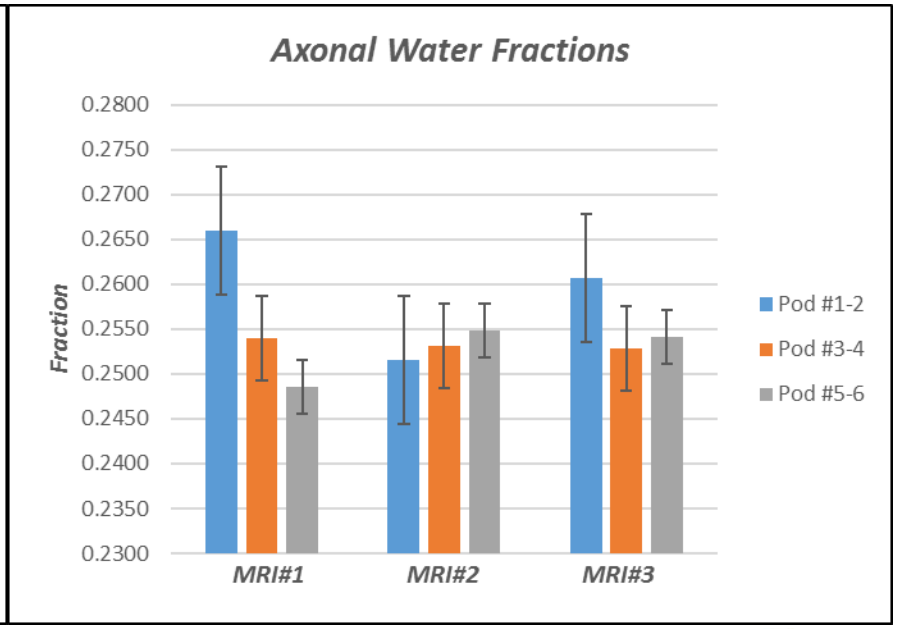
Swine Model Phase 2 Nonsedated

- *Phase 2 model to mimic U-2 pilot experience*
  - *Nonsedated subjects with 1-hour prebreathe, 30-minute ascent to 30k, 8 hours at altitude, 30-minute descent*
  - *Behavioral observation during flights*
  - *MRI and inflammatory/genomic/proteomic markers to measure injury*
  - *Subsequent tissue examination and live-cell neurophysiological studies*
  - *Study commenced 1/2016*
- *Three limbs*
  - *30k feet altitude/95+% O_2*
  - *5k feet altitude/room air*
  - *785 feet altitude/95+% O_2*

Kurtosis Diffusion Swine Model Phase 2

- ***Significant increase in exposed population kurtosis MRI#2 with return to baseline MRI#3 (p<0.001)***
  - ***GLM (with age as a covariable) & repeat measure linear model (rANOVA)***
- ***Decrease in axonal water fraction MRI#2 with return to baseline MRI#3***
- ***Consistent with increase in interstitial water (edema) with axonal injury and increased blood flow related to hypobaric exposure***
- ***Preliminary path data normative (n=2; axonal stains pending)***





NDCS Hypothesis

- ***Hypothesis: N_2 gas bubble release associated with decrease in ambient pressure initial inciting event (decompressive stress)***
- ***Transient increase in CBF that persists at 72 hours post-exposure***
  - ***Neurochemical metabolite change suggests neuronal and glial cell injury***
- ***Possibly the pre-existing levels of neurometabolites suggest an underlying susceptibility to injury***
- ***Recurrent exposure leads to proton (H_2O) increase***
  - ***Hypothesize that sufficient stress leads to discrete WMH burden and diffuse axonal decrement***
- ***Associated neurocognitive changes reflect the diffuse axonal degradation***
- ***Possibly certain individuals are more susceptible***
  - ***Potentially may be able to identify those that are more susceptible.***

Questions ?