Aircrew Training Hypoxic Hypobaria Elevated Cerebral Blood Flow – When Does it Return to Normal?

NATO STO 19 Mar 2019

DR. (COL RET) PAUL SHERMAN, MD, FACR
COL JOHN SLADKY, MD, FAAN
DR. BIANCA CERQUEIRA, PHD

Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Disclaimer Information

- No financial relationships to disclose.
- No discussion of off-label use and/or investigational use in my presentation.
- 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.

Radiologist/Neuroradiologist
Former Senior Flight Surgeon

U.S. Air Force photo by A1C Zade C. Vadnais

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Overview

- Background Studies
  - U-2 pilot, physiologist, and normative database study *(2011-2014)*
    - 105 U-2 pilots, 89 aerospace physiology chamber inside observers (AOP), 148 controls
  - Single hypobaric exposure study *(2014-2017)*
    - 96 Aircrew Fundamentals Course (AFC) trainees, 65 controls, 14 AOP
- “Duration of Effects” study *(2018-2019)*
  - *30 AFC trainees to date*
- *Summary*

USAF photo by A1C Bobby Cummings

Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Military and Civilian Relevance

- Potential impact to anyone subjected to decompressive stress
  - High altitude drops (special forces, aircrew)
  - High altitude operations in unpressurized platforms (including rotary)
  - SCUBA divers
  - NASA astronauts
- Long-term neurocognitive functioning impact/disability in exposed individuals remains unknown
- Aeromedical transport personnel of neurological worsening in acute TBI associated with flight (human and animal studies) and in worsening with hypobaria only (swine)
- Increase in unexplained physiologic events (UPEs)

USAF photo by Chris Gulliford

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Overview

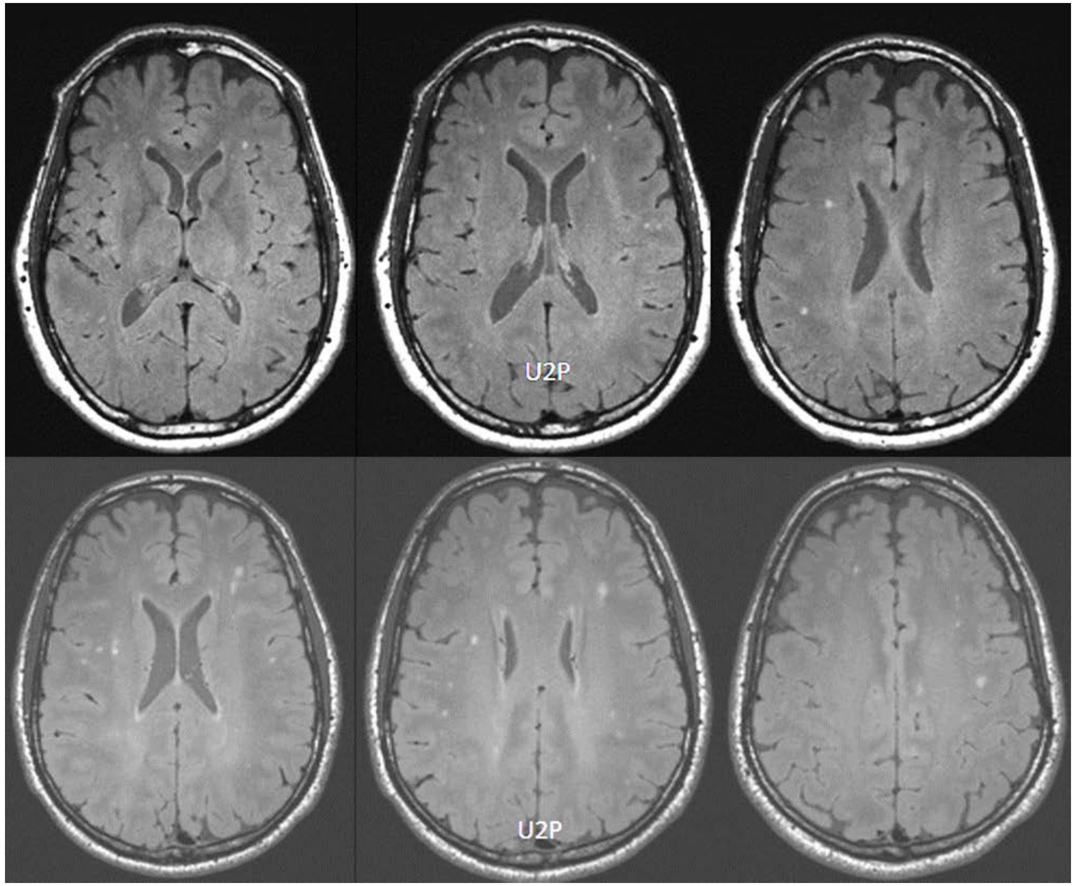
- U-2 pilot, physiologist, and normative database study *(2011-2014)*
  - 105 U-2 pilots, 89 aerospace physiology chamber inside observers (AOP), 148 controls
  - Neurologic decompression sickness; white matter integrity; microcognitive changes
- Single hypobaric exposure study *(2014-2017)*
  - 96 Aircrew Fundamentals Course (AFC) trainees, 65 controls, 14 AOP
  - CBF changes
- “Duration of Effects” study *(2018-2019)*
- Summary

USAF photo by A1C Bobby Cummings

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

U-2 Study – Repetitive Exposure

- Imaging began as part of evaluation for NDCS
- Focal punctate white matter hyperintensities (WMHs) on FLAIR MRI
  - U-2 Pilots and altitude chamber inside observers (AOP)
- Global decrease in white matter integrity in U-2 pilots as measured by MRI diffusion tensor imaging (FA)
- Microcognitive changes in U-2 pilots compared to other USAF pilots
- MRI evaluation is quantitative and highly reproducible



U2P and AOP, with or without NDCS

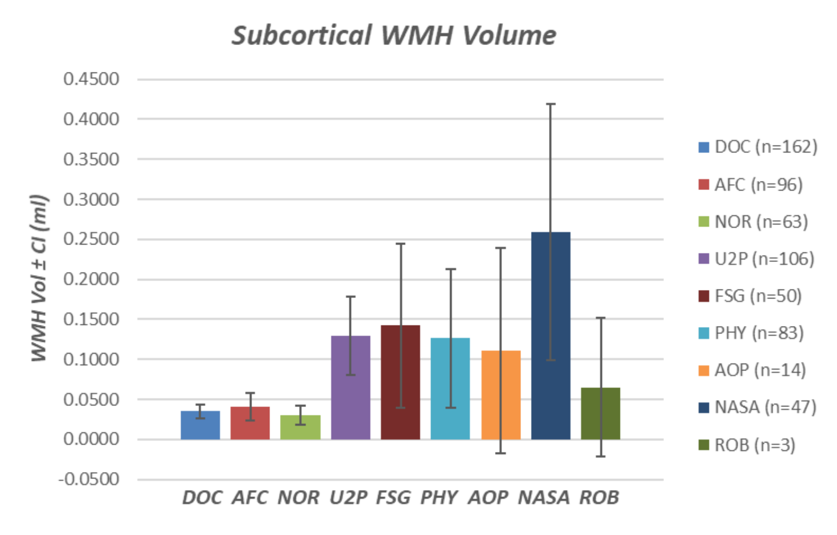
Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

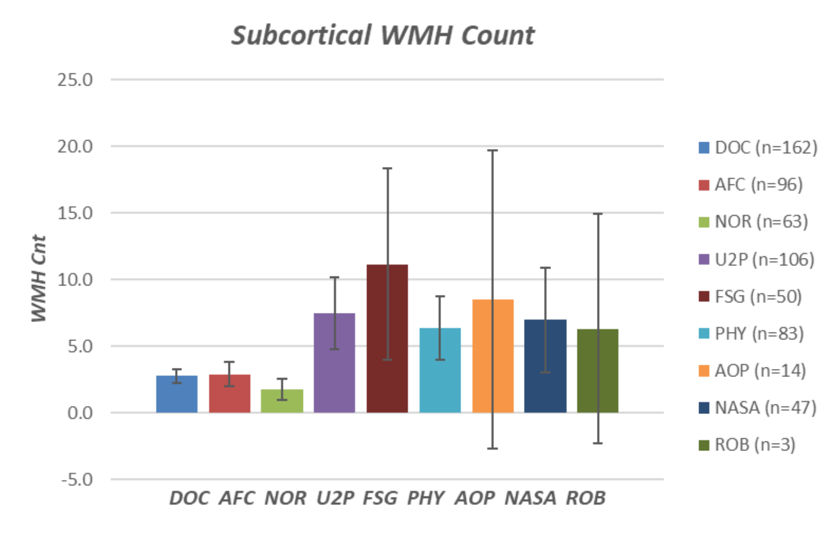
Phase 1 Repetitive Exposure White Matter Hyperintensities

- Significantly increased subcortical WMH volume/count in U2P & AOP/PHY
- AFC ≈ DOC ≈ NOR
- U2P ≈ AOP/PHY ≈ FSG
    - Individual variability
- Volume most clinically significant

	DOC	U2P	PHY
WMH vol (mean±CI)	0.035±0.009	0.129±0.049	0.126±0.086
WMH cnt	2.8±0.5	7.5±2.7	6.4±2.4
Mann-Whitney-Wilcoxon	DOC:PHY	DOC:U2P	U2P:PHY
WMH volume (mL)	p=0.0287	p<0.0001	p=0.4046
WMH cnt	p=0.0499	p=0.0374	p=0.9388

DOC – doctorate controls
U2P – U-2 pilots
AOP/PHY – aerospace operational physiologists
AFC – aircrew fundamental course students
NOR – combat arms students
FSG – flight surgeons
NASA – astronauts
ROB – reduced oxygen breathing device



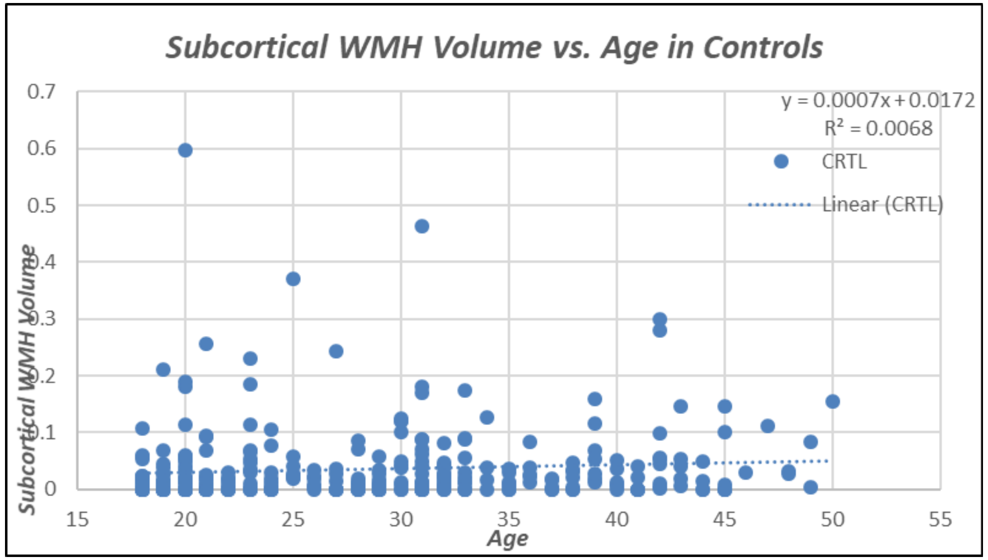


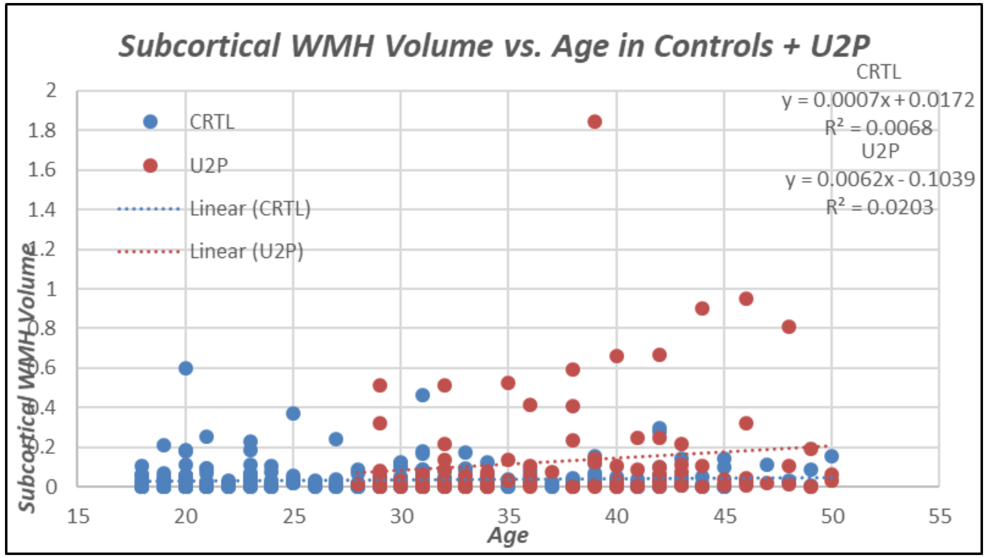
McGuire et al. Neurology. 2013; 81:729-735
McGuire et al. Ann Neurol. 2014; 76:719-726

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Subcortical WMH Volume vs. Age

- Subcortical WMH volume known to increase with advanced age (> ~ 60 yr)
  - Over age range 18-50 essentially no increase with age
- Increase slightly more rapid in U2P but not sufficient to account for increase in volume
  - Suggests not a simple factor of exposure

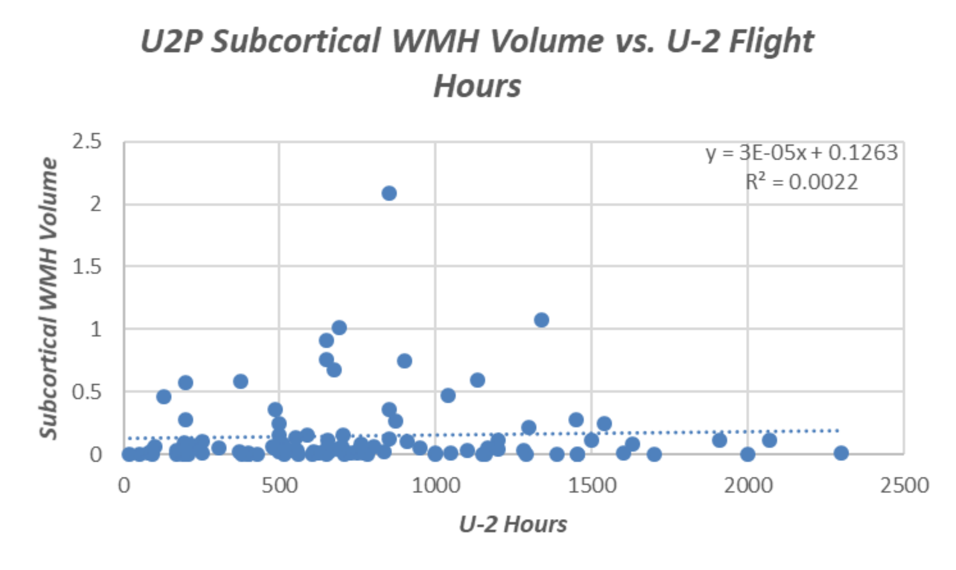


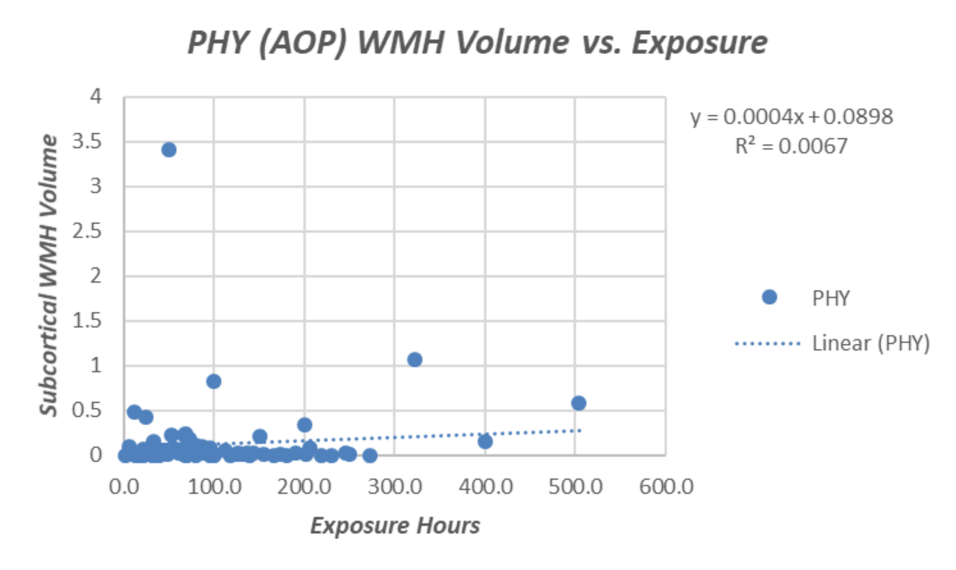


Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

WMH Volume vs. Exposure

- Little correlation between total hours of exposure and subcortical WMH burden
  - Suggests multifactor relationship to WMH burden
- Mild/controlled HTN and/or hyperlipidemia not an explanation for findings in this study population
- No significant contributing factors
  - No caffeine, smoking, supplements, etc.
  - Possible operations tempo factor

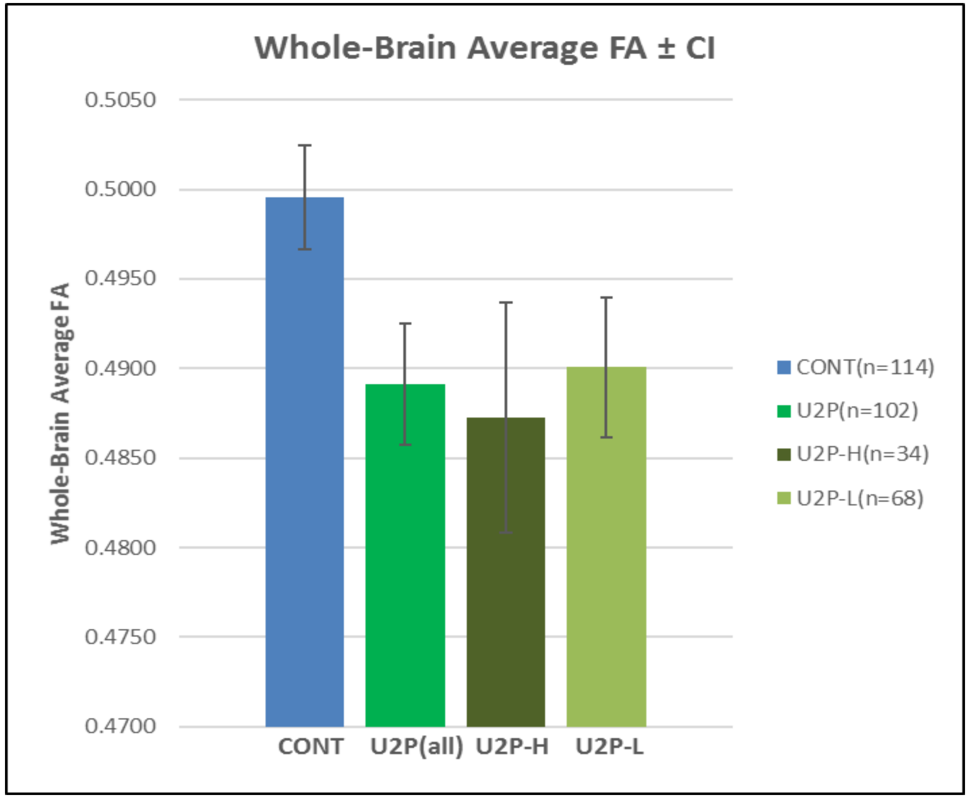




Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Repetitive Hypobaric Exposure Fractional Anisotropy (FA)

- Whole-brain average FA assesses entire WM
    - FA believed to correlate with axonal integrity
    - Used ENIGMA-DTI protocol to exclude visible areas of WM injury (punctate WMH)
    - KS $p<0.001$; GLM $p<0.001$
        - Kolmogorov-Smirnov (KS)
        - Generalized linear model (GLM) with age as nuisance covariate
- Reflects ~ 2% decline in axonal integrity
- Decline in axonal integrity appears to track with WMH burden
- Results contingent upon cross calibration of scanners
    - *46 subjs dual imaged (r=0.85; COV=4%). UT and Wilford Hall magnets



McGuire et al. Aerosp Med Hum Perform. 2016; 87(12):983-988

Phase 1 Repetitive Exposure Neurocognitive Differences

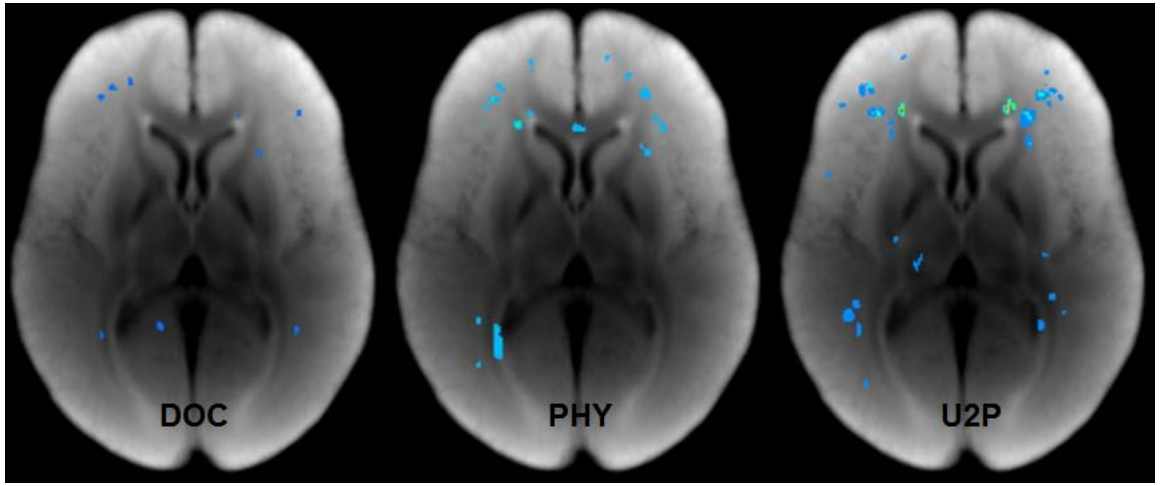
- Significant decrease in current computer-based Microcog testing in U2P compared to AF pilot controls
- Pattern of change similar to all other neurological diseases with subcortical brain injury
- Multiple indices indicate that all pilots are similar at UPT
- Decrease suggests diffuse white matter process

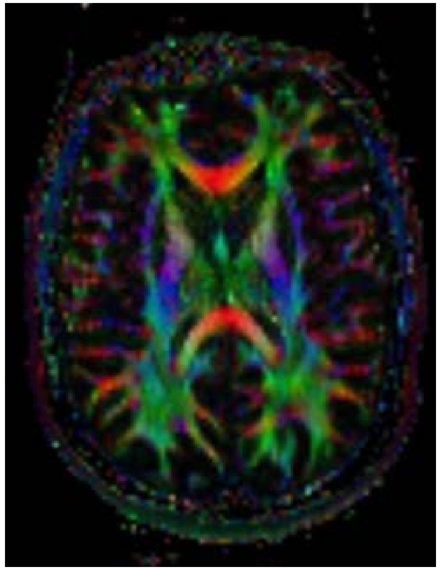
	MicroCog	U2P (n=93)	AFP (n=80)	t-test (2-tailed) Significance	Sidak (2-tailed) Significance
1	Attention/mental control	104.4	103.8	p=0.696	p=0.997
1	Reasoning/calculation	99.4	106.5	p<0.001	p=0.001
1	Memory	105.5	110.9	p=0.007	p=0.036
1	Spatial processing	109.1	109.1	p=0.989	p=1.000
1	Reaction time	107.3	104.8	p=0.047	p=0.216
2	Information processing speed	103.6	106.5	p=0.100	p=0.189
2	Information processing accuracy	102.1	105.8	p=0.016	p=0.032
3	General cognitive functioning	103.5	108.5	p=0.002	p=0.004
3	General cognitive proficiency	105.4	108.6	p=0.037	p=0.072

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

U-2 Study – Summary

- Recurrent exposure to nonhypoxic extreme hypobaria incites:
  - Focal punctate WMH on MRI
  - Diffuse decrement in axonal integrity on MRI (FA changes)
  - Acquired neurocognitive decline as measured on CBT
    - Corresponds to WMH burden
- Quantitative MRI highly reproducible





Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Operation Changes Based upon Research Findings

- “Maintenance MRI program” for U-2 pilots
    - Currently no MRI screening for AOP
        - Decision made by USAF/SG
- Mission tempo changes, 72 h between ops
    - For U-2 pilots and AOP
- CARE (cabin altitude restriction effort) – 15K for single seater

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Single Exposure Study

- Hypothesis – single occupational exposure to hypobaria and/or hypoxia will be associated with transient MRI and serological changes
- Identifying transient changes with single exposure may lead to understanding the neuropathophysiology of white matter injury demonstrated in chronic hypobaric exposure
  - In combination with animal studies
- Only occupational training hypobaric and/or hypoxic exposures per USAF/SG (LTG Travis)
- September 2014 – August 2017
- 96 Aircrew Fundamentals Course (AFC) trainees, 65 controls, 14 AOP, 3 ROBD

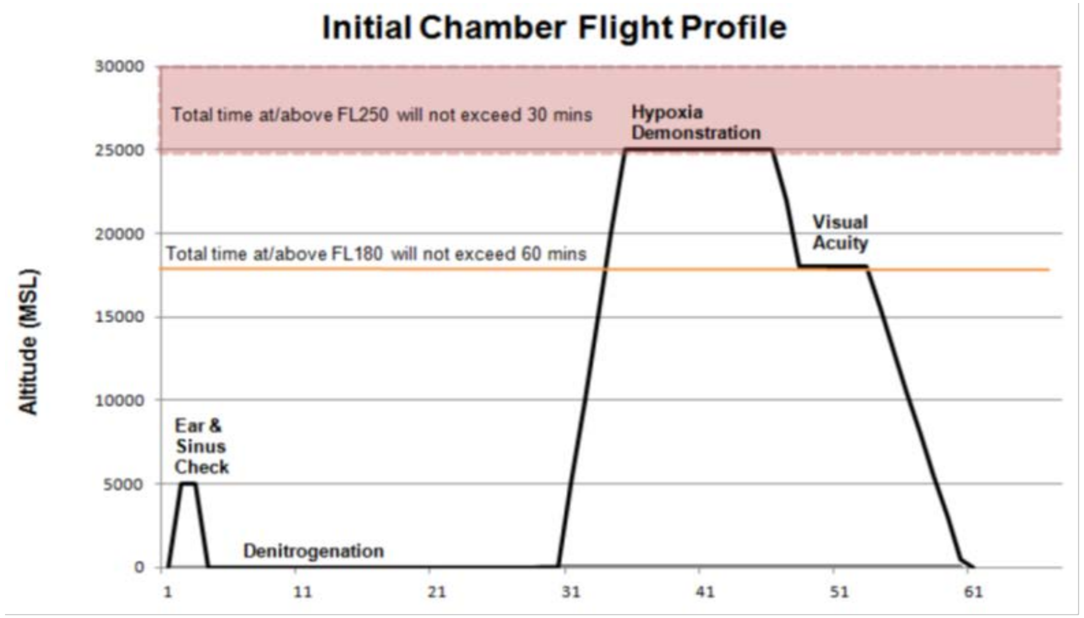
Photo by 59MDW/PA

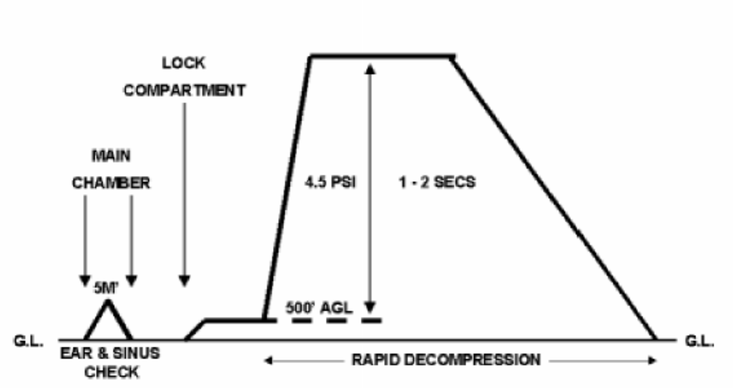
Single Exposure Study

- Examine acute (MRI/serological) changes following a single exposure – all meet FCII/FCIII neurological standards
  - 1. Hypobaric-hypoxic (AFC – aircrew chamber training) – n = 96
  - 2. Hypobaric (AOP inside safety monitors) – n = 14
  - 3. Hypoxic (ROBD – reduced O_2 breathing device) – n = 3
  - 4. NOR – Controls –n = 65
    - All subjects with baseline/control MRI prior to exposure so our normative database is approx. n = 400
- Protocol:
  - MRI 24 h before; 24 h after; 72 h after
  - Serological immediately before; immediately after; 24 h after; 72 h after
  - No other altitudinal exposure beginning 7 d prior*
  - No alcohol beginning 7 d prior*
  - Maintain normal physiological activities
    - No sleep deprivation/shift changes, etc.
- Intra-subject and cross-group comparisons

USAF Chamber Profile

- Max altitude 25,000 ft
- (7,620 m, 5.45 psi)
- 30-min denitrogenation
- Time >FL250 ≤30 min





AFI11-403 30 Nov 2012

USAF photo by Benjamin Faske.

USAF photo by Joel Martinez.

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Cytokine/mRNA Pending Analysis

- Human (and swine studies) evaluating inflammatory markers
  - 59^{th} Clinical Investigations and Research (CIRS)
- Preset cytokine panels
  - Multiplex panel
- mRNA upregulation / downregulation
- Swine studies include CSF
  - US guided LP
- Limitation – no bioinformatics staff at Wilford Hall
  - Contracting Univ of Texas Health Science Center

Swine (CSF/Serum)	Human (Serum)
GM-CSF (granulocyte macrophage stimulating factor)	GM-CSF
IFNγ (interferon gamma)	IFNγ
IL-1α (interleukin 1-alpha)	IL-10
IL-1rα (interleukin 1 receptor alpha [one])	IL-12
IL-1β	IL-13
IL-2	IL-1β
IL-6	IL-2
IL-8	IL-4
IL-10	IL-5
IL-12	IL-6
IL-18	IL-7
	IL-8
TNFα (tumor necrosis factor)	TNFα
S100B (S100 glial specific calcium binding factor)	S100B

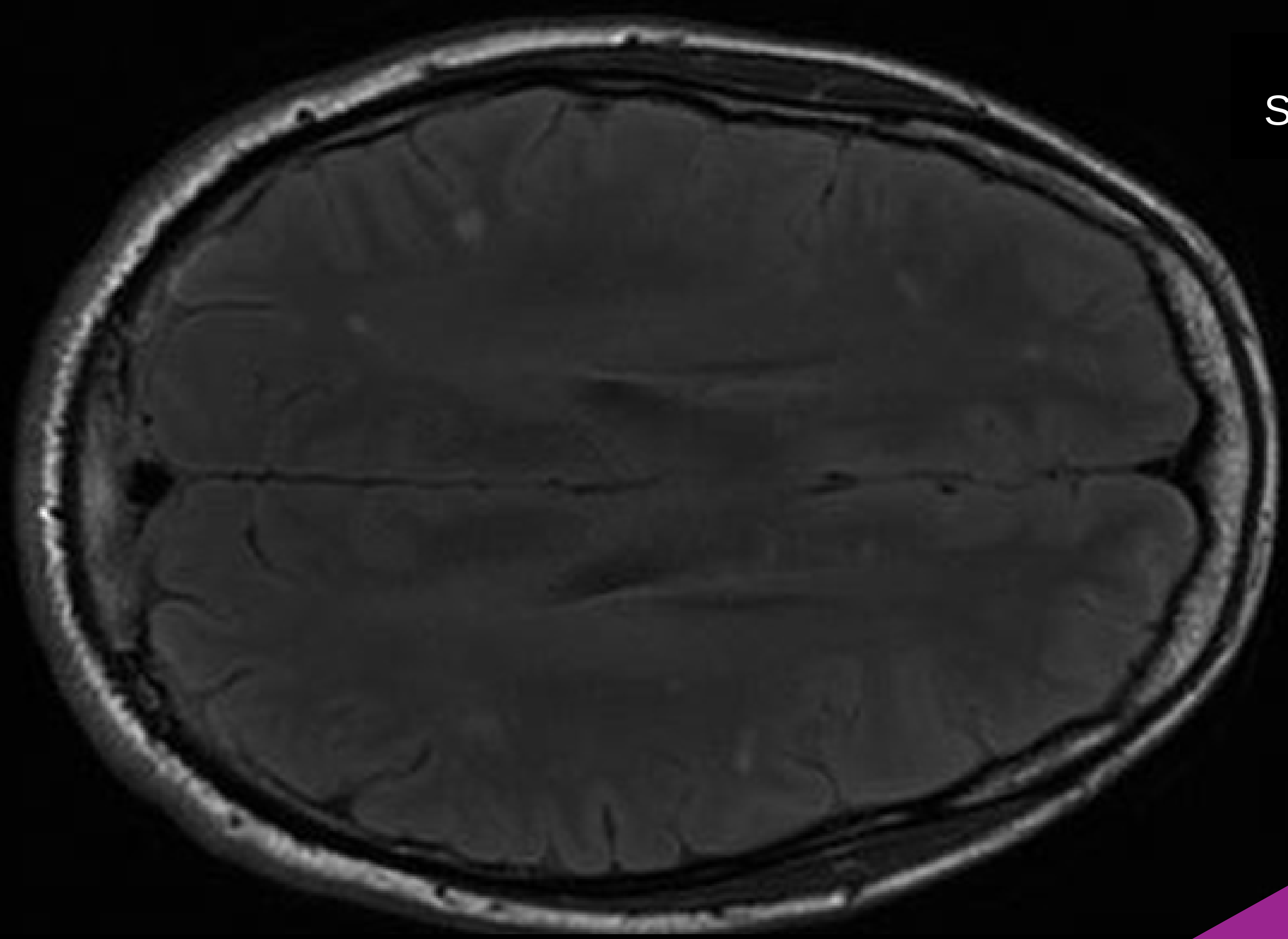
Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

NATO HFM Research Task Group 274 – "Forward Together"

- **The Impact of Hypobaric Exposure on Aviators and High-Altitude Special Operations Personnel**
- Began as 1-yr Exploratory Team in July 2015
- RTG July 2016 – Sep 2021 (recently extended)
- 9 member nations
- Individual nation and collaborative research is ongoing

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

White Matter Hyperintensities and Implications for Future Altitude Chamber Research



International Congress of Aviation and Space Medicine 2018, Bangkok, Thailand

Thursday 15th November 2018

Dr Des Connolly

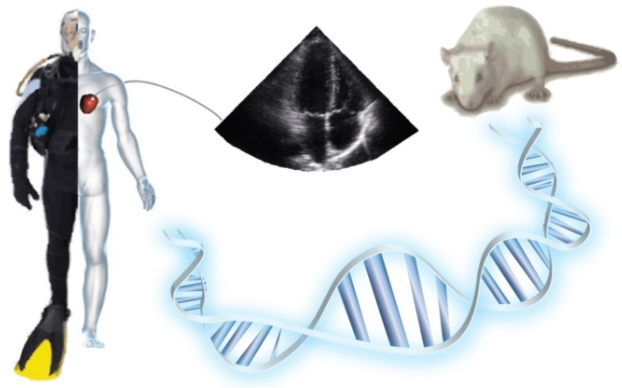
QINETIQ

U2 flying rats at NTNU

Preliminary Results from DTI

Andreas Møllerløkken, Marianne Bjordal Havnes and Marius Widerøe

Norwegian University of Science and Technology



5th HFM-RTG-274 MEETING PARIS, FEBRUARY 2019

”CONSEQUENCES OF REPEATED EXPOSURES TO HYPOBARIC HYPOXIA

WITH REGARD TO THE PERSONNEL´S HEALTH

–

AN EXPLORATORY STUDY IN HIGH ALTITUDE CHAMBER PERSONEL”

C. LEDDERHOS AND F. WEBER

Centre of Aerospace Medicine
of the German Air Force

Canadian Study Update:

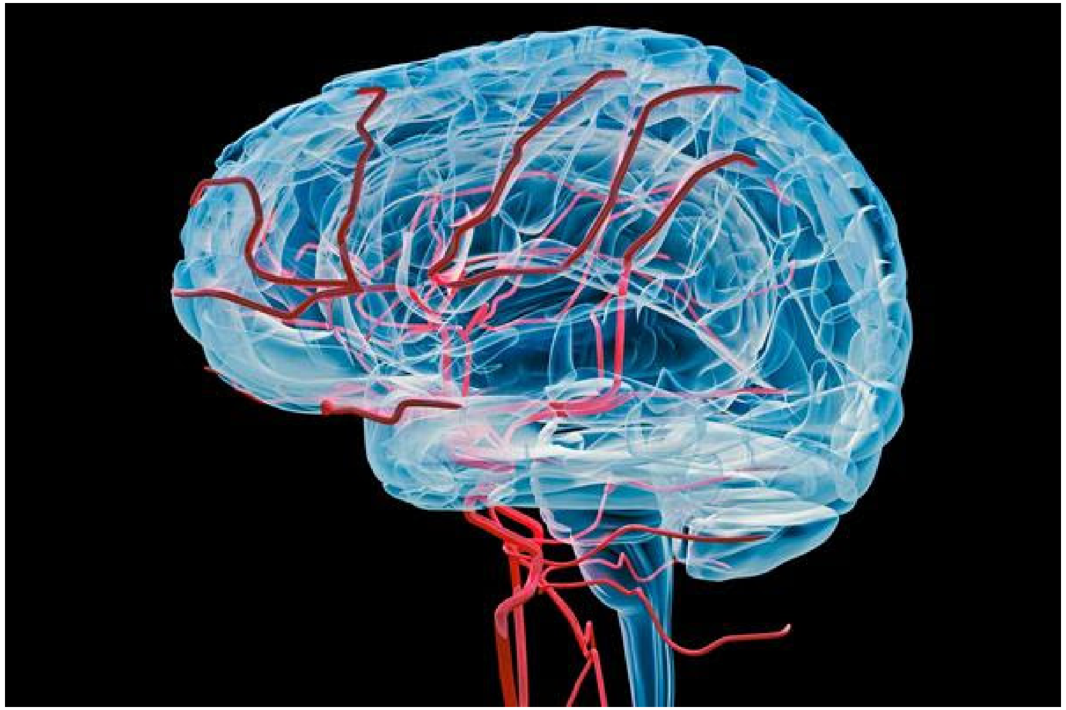
Prevalence and Correlates of White Matter Hyperintensities in RCAF Aircrew and Other Related Trades

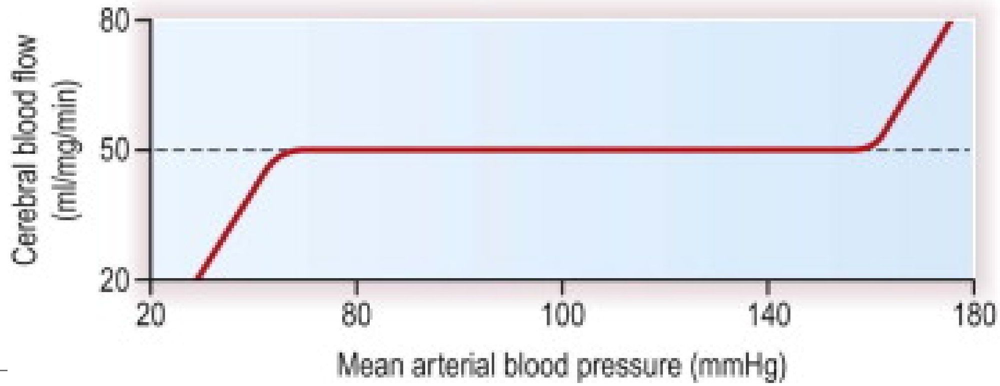
Joan Saary, MD, PhD, FRCPC
CFEME Consultant in Occupational Medicine
(Canadian Forces Environmental Medicine Establishment)
Assistant Professor of Medicine, University of Toronto

NATO RTG 274

Cerebral Blood Flow – Why is it Important?

- Normal, normotensive CBF is approximately 5-7 mL per 1gm of brain tissue per minute (50-70 mL/100mg/min)
  - Given normal cerebral perfusion pressure (CPP) range of 60 – 100 mmHg
  - If outside normal CPP, then based upon mean arterial pressure (MAP)
    - Significance in polytrauma, etc.





Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Cerebral Blood Flow – Why is it Important?

- CBF is autoregulated
  - Brain needs a constant blood supply and water homeostasis
  - There is a high metabolic demand of neuronal tissue
  - Tight coordination between neuronal activity and blood flow
  - Brain parenchymal arterioles have considerable basal tone which contributes to vascular resistance in the brain
  - There are “coordinated” blood flow responses in the brain

“You’re right, there wasn’t much blood getting to his head”

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Cerebral Blood Flow – Why is it Important?

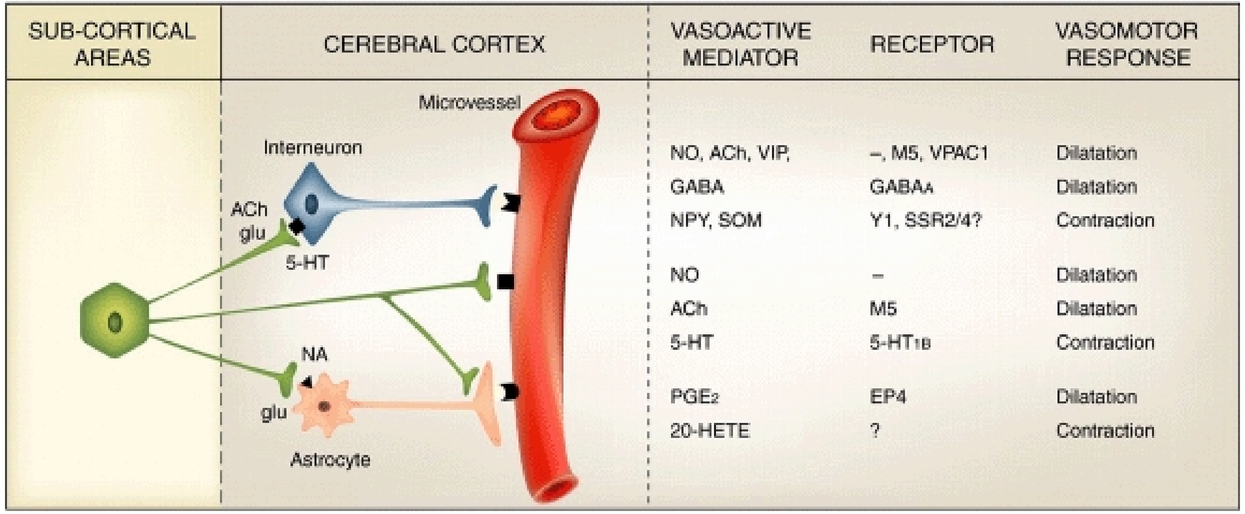
- Relevance in the aerospace environment
  - Increased metabolic demand increases CBF
  - Aerospace environment factors
    - Hypoxia, CO_2
- Research application to evaluate CBF in our studies
  - Strong clinical application in stroke image
    - CBF, CBV, TTP, Tmax

"I probably won't be asked to be the first brain donor."

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Cerebral Blood Flow – Why is it Important?

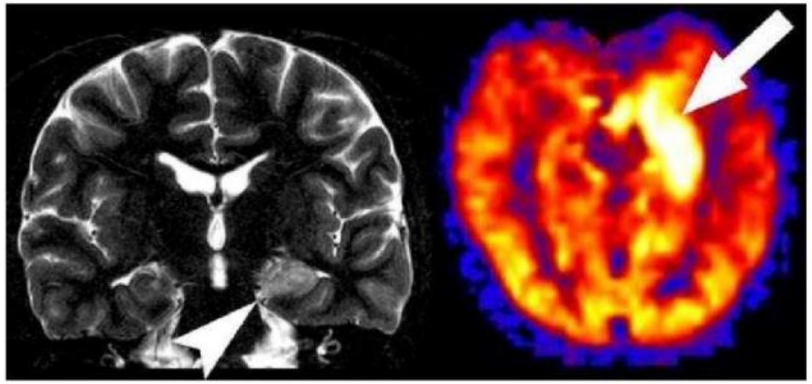
- Sources:
  - Acute hypoxia (and chronic)
    - pO_2 < 50 mmHg
    - Decreases ATP levels, increases nitric oxide and adenosine production => vasodilatation
  - Increased carbon dioxide (CO_2)
    - Causes marked dilatation of cerebral arterioles/arteries
      - 7% CO_2 inhalation will decrease CBF by up to 100%
    - Decreased CO_2 causes vasoconstriction and decreased CBF
    - Effects believed to due direct impact of extracellular H+ on vascular smooth muscle



MRI Arterial Spin Labeling (ASL) Technique

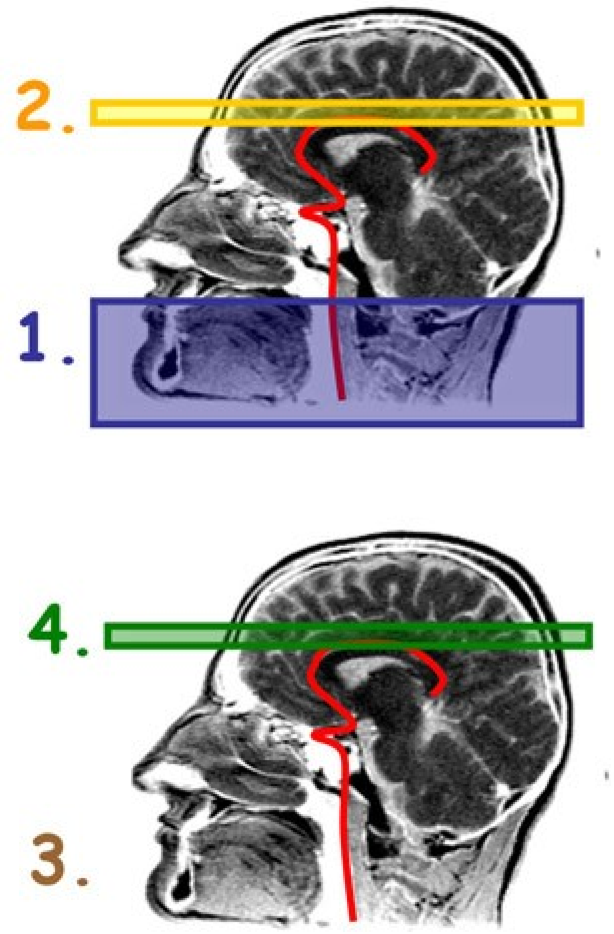
- ***No i.v. gadolinium contrast required***
- ***Quantitative technique (vs. qualitative)***
- ***Computer post-processing required***
- ***Physics concept:***
  - ***Labeling" of protons in the blood (water) of supplying vessels outside imaging plane***
    - ***"Magnetic tagging" of inflowing blood***
  - ***Image brain in the labeled and control (unlabeled) state***
  - ***Subtraction of labeled and controlled images***
  - ***Quantitative perfusions maps can be performed (GM, WM)***
  - ***Reproducible, reliable; comparable to PET imaging***
- ***Results in a signal proportional to local cerebral blood flow (CBF)***
  - ***mg/100 g/min (or mg/1 gm/min)***

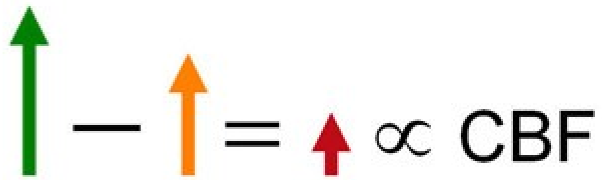
- ***Hippocampal seizure focus - hyperperfused***
- ***Magn Reson Imaging Clin N Am. 2009 May; 17(2): 315–338.***



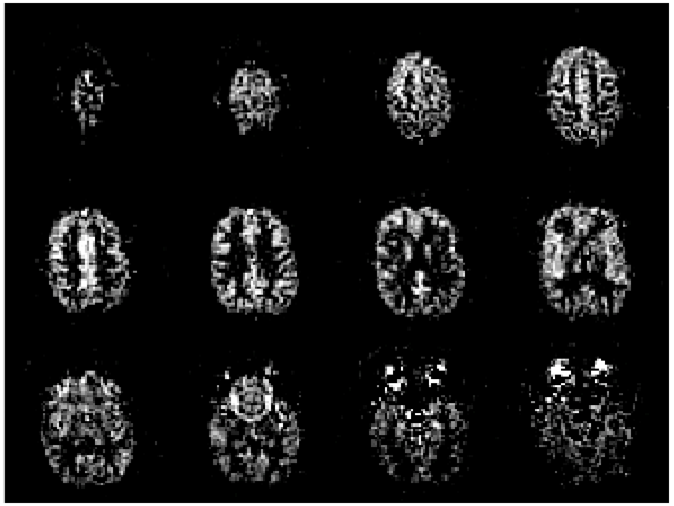
ASL Technique – Steps

1. Tag inflowing arterial blood; 2. Acquire tag image; 3. Repeat without tag; 4. Acquire control image; 5. Subtract control-tag image



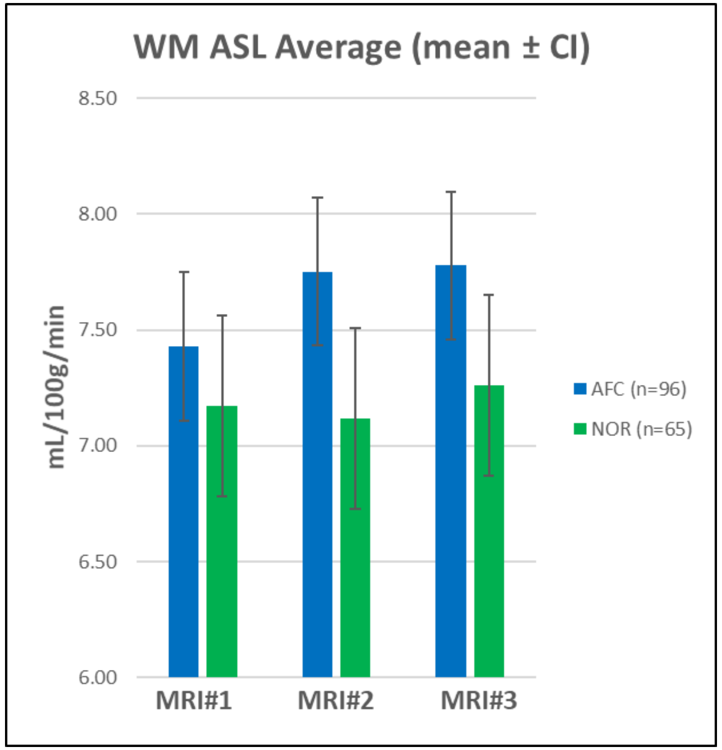


5.

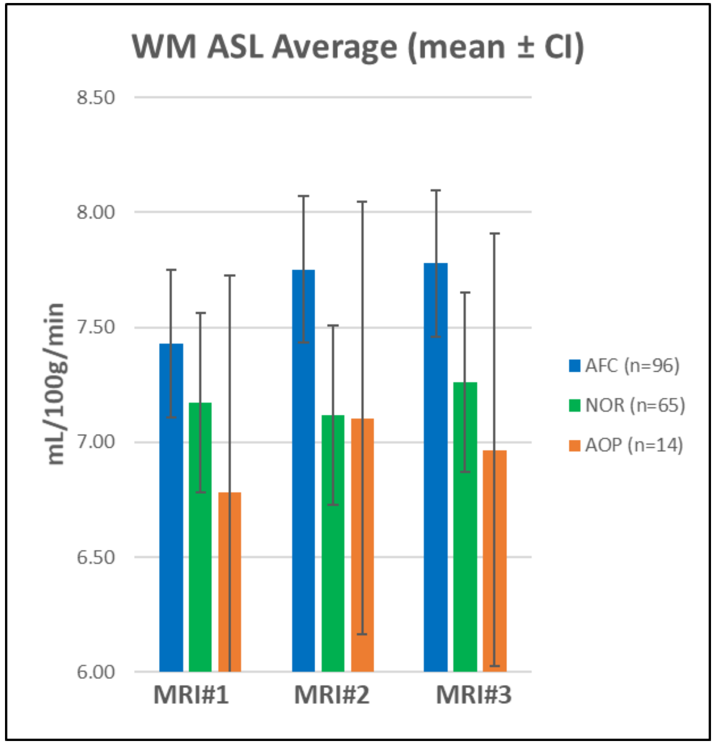


Arterial Blood Flow (ASL) – Cerebral Blood Flow (CBF)

- Increase in WM CBF at 24/72 h
  - Significant group (AFC vs. NOR) difference
    - WM p<0.001 (Utilized generalized additive model adjusted for age and gender)



AFC	Subj #	WM
MRI#1 avg	96	7.43
MRI#2 avg	94	7.75
MRI#3 avg	96	7.78
TTEST #1-#2		0.004
TTEST #1-#3		0.009
TTEST #2-#3		0.967
NOR		
MRI#1 avg	65	7.17
MRI#2 avg	65	7.12
MRI#3 avg	60	7.26
TTEST #1-#2		0.738
TTEST #1-#3		0.363
TTEST #2-#3		0.088



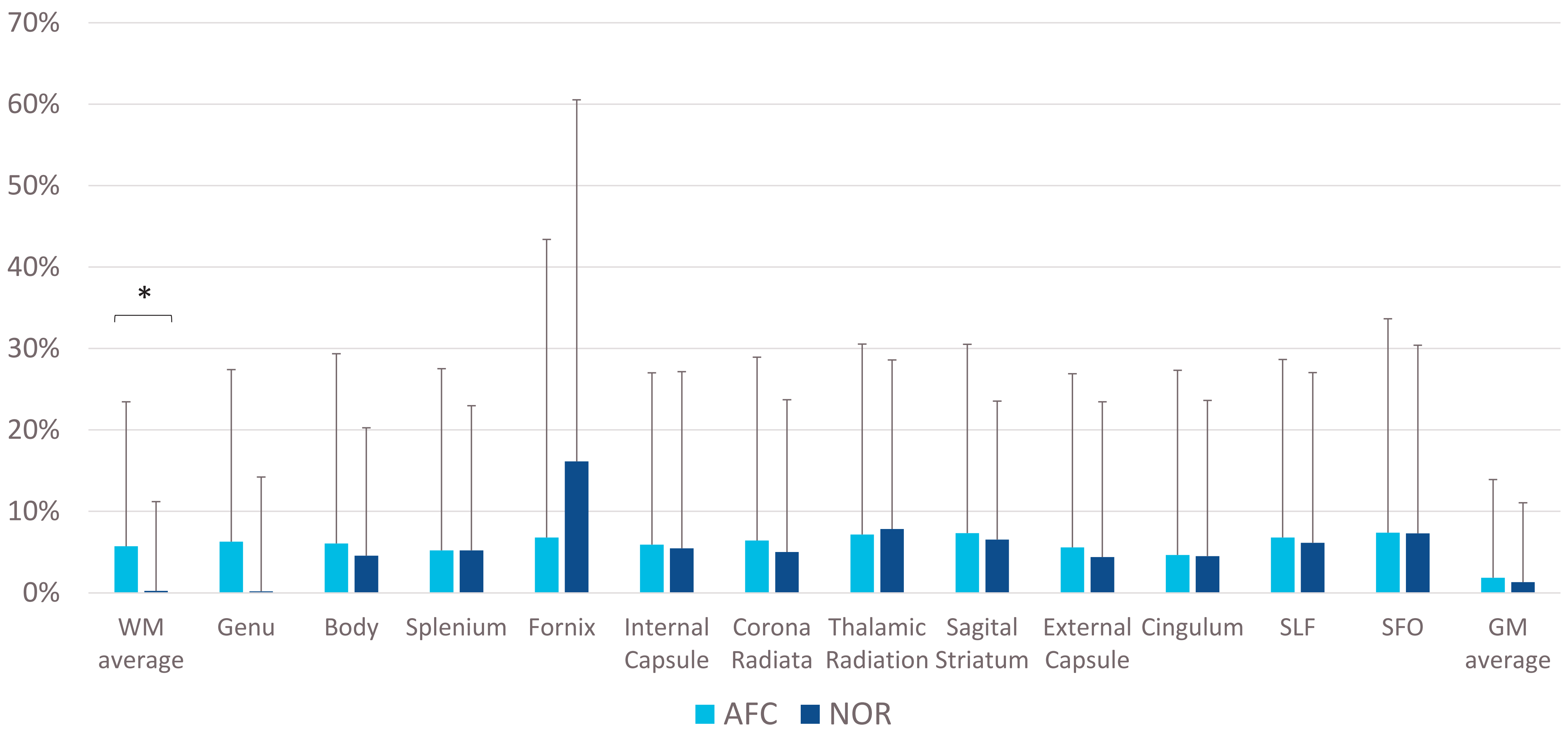
Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Duration of Effects Study

- Same Aircrew Fundamentals Course volunteers (occupational training)
- 5 MRI data points
  - Determine duration of increased CBF and when return to normal post single occupational exposure to 25,000 ft
- Baseline (-24h), exposure +24h, +72h, +120h, +168h
- Recruitment challenging
  - Duration of study conflicts with post AFC course career field assignments
- Analysis of n=21 to date; imaging of n = 30

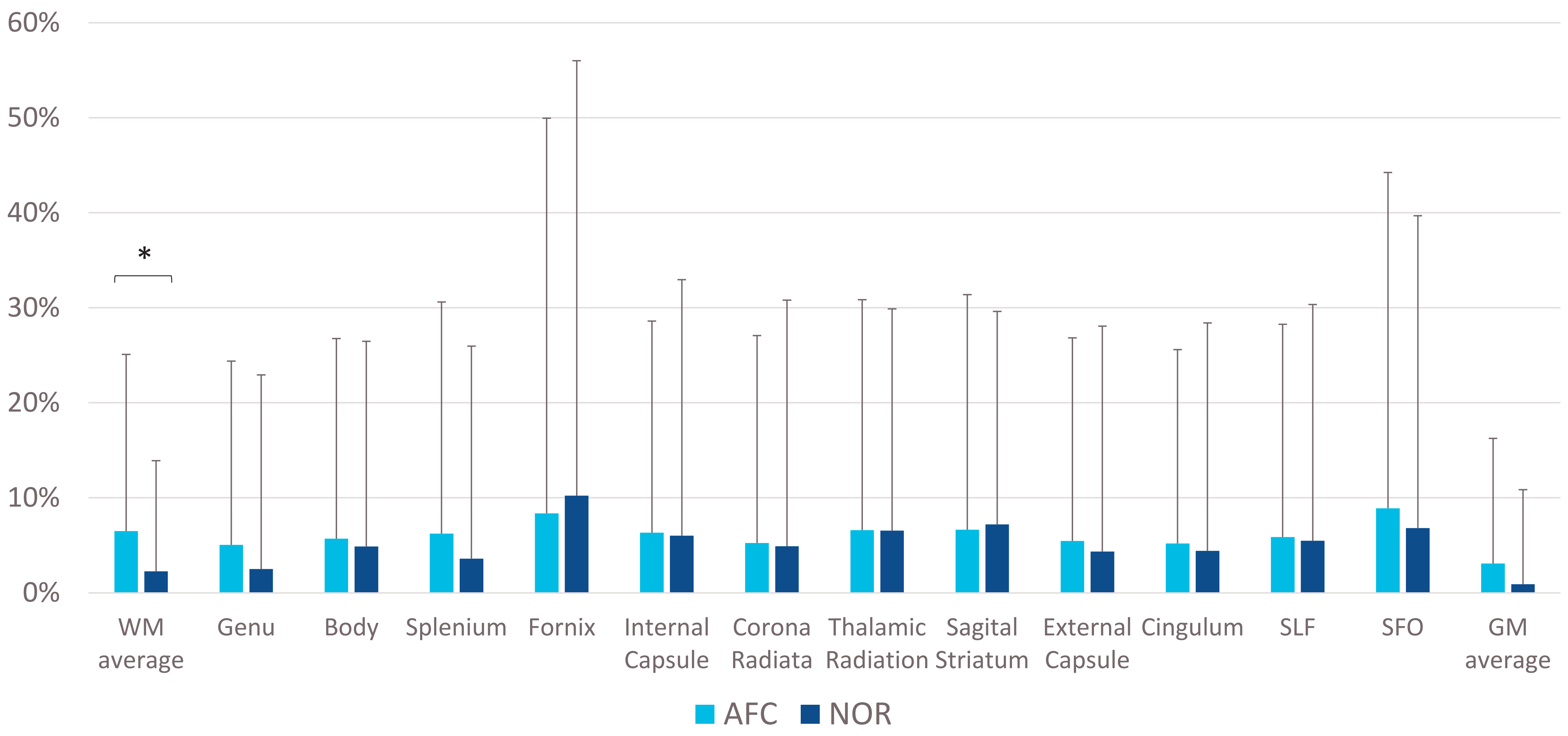
Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Results – CBF percent change from baseline at 24 hours



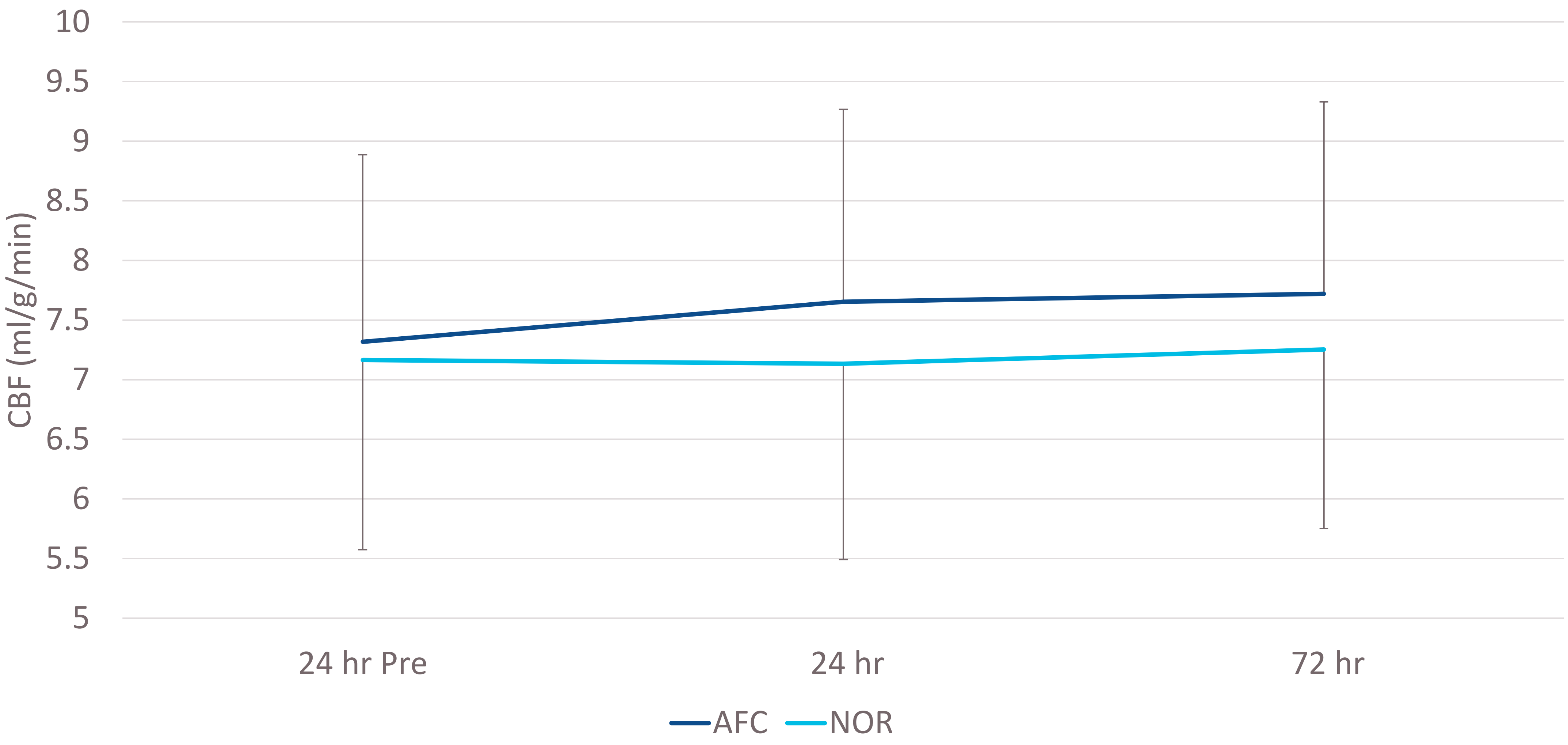
Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Results – CBF percent change from baseline at 72 hours



Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

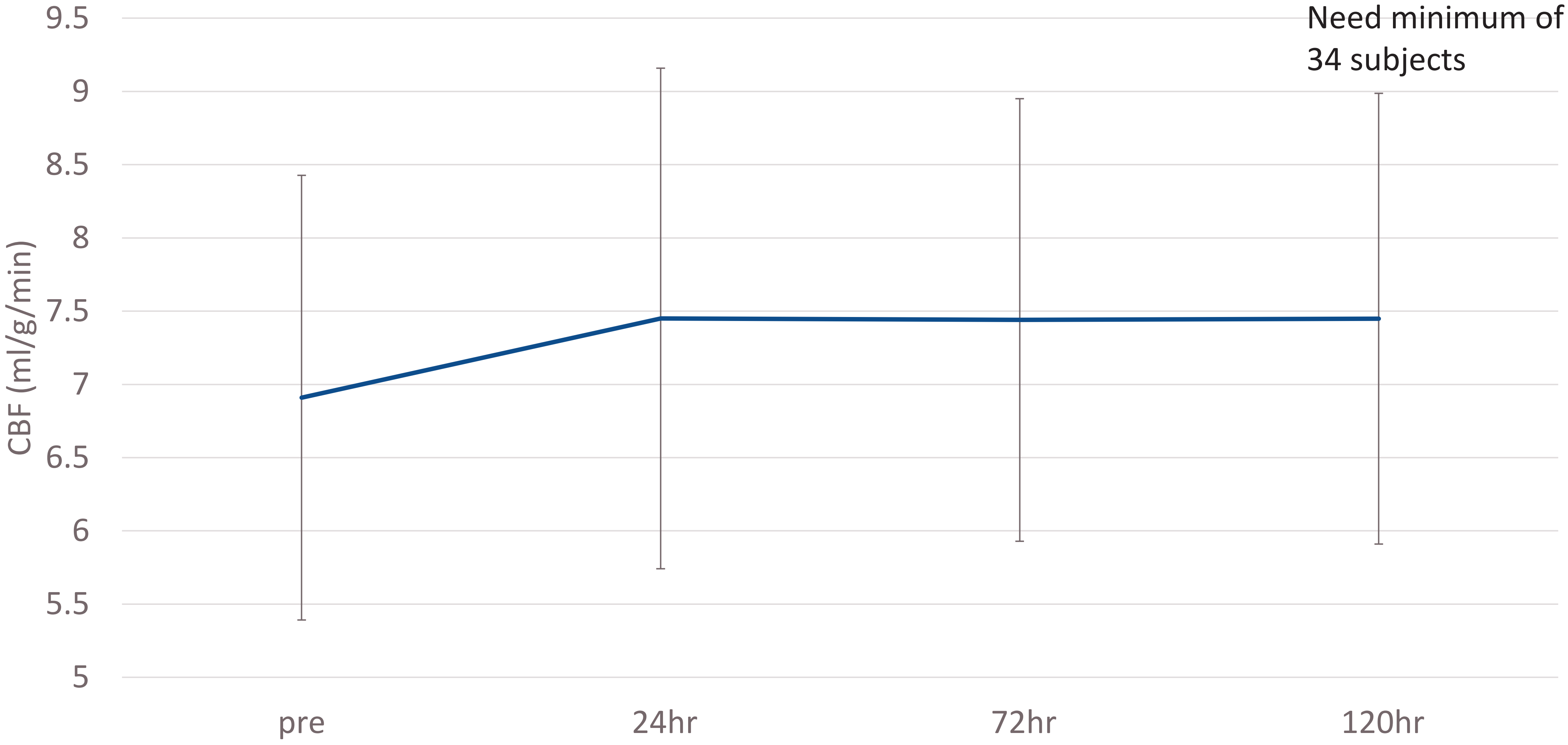
Results – White Matter Average CBF



Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Results – AFC2 (duration study) white matter average CBF

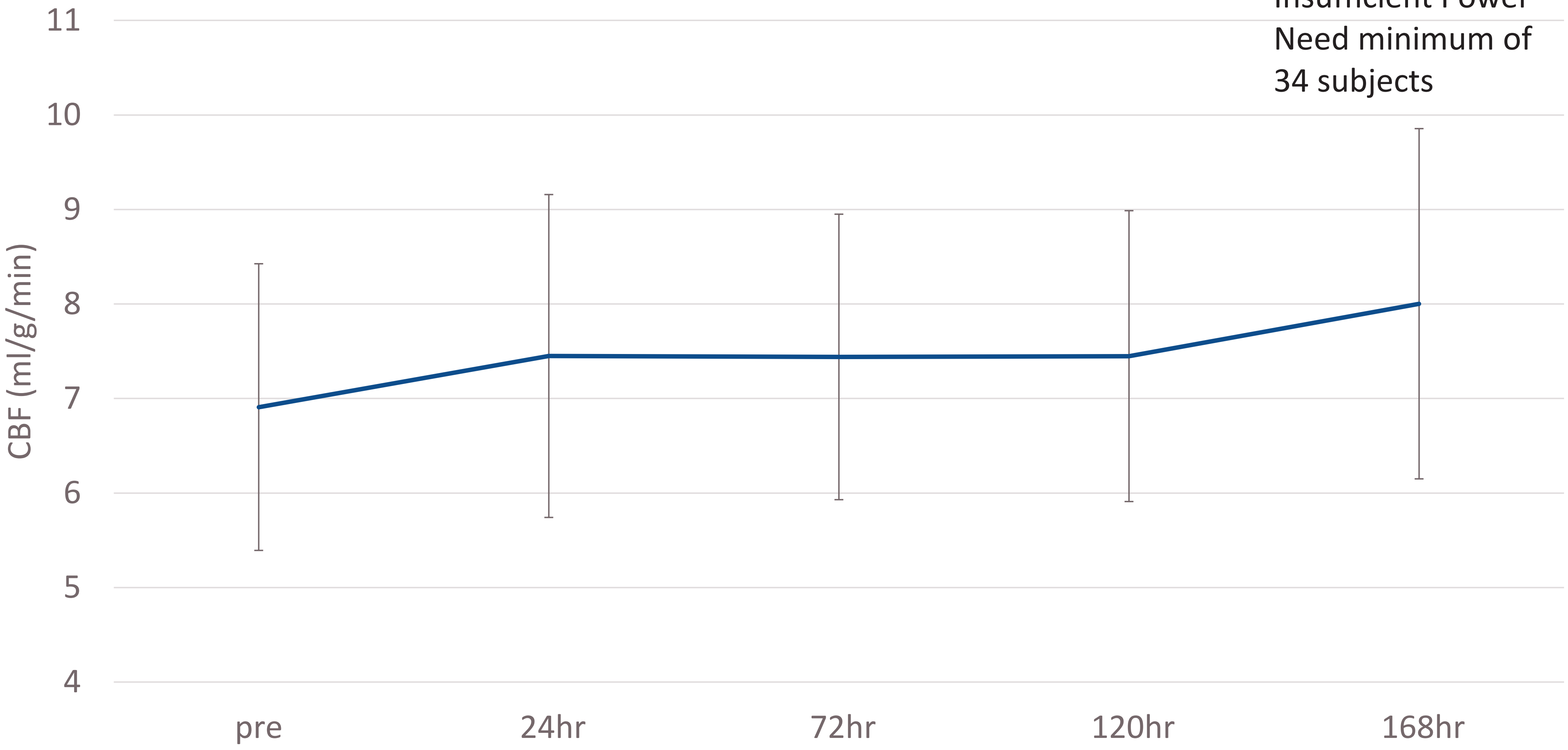
n = 21
Insufficient Power
Need minimum of 34 subjects



Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Results – AFC2 white matter average CBF

n = 21
Insufficient Power
Need minimum of
34 subjects



Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Conclusions

- A single exposure to hypoxic hypobaria in routine altitude chamber training demonstrates an increase of WM CBF 24 h post-exposure that persists at 72 h
    - Hypoxic portion ~ 2-5 min (correlating with a PaO_2Sat ~ 65-75%)
    - We know acute hypoxia increases CBF
- This reflects an increased metabolic demand and may represent a transient cerebral injury has occurred

Cleared, 88PA, Case # 2019-xxxx, xx Jan 2019.

Conclusions

- The greater the initial WMH burden appears to be associated with a greater the ASL response
  - Inherent predisposition for injury?
  - No correlation with ApoE (E2 and E4 alleles) genomics study and U-2/AOP
    - 92 subjects
    - Recently published 2018
      - Chapleau, RR, Martin CA, Hughes SR, Baldwin JC, **Sladky JH**, **Sherman PM**, Grinkemeyer M. Evaluating apolipoprotein E genotype status and neuroprotective effects against white matter hyperintensity development in high-altitude careers. BMC Res Notes. 2018 Oct 25; 11 1): 764. doi: 10.1186/s13104-018-3867-7

Conclusions

- Insufficient sample size at this time to determine if increase in CBF is sustained for longer than 72 hours
  - Trend suggests return to baseline at 120 hours but few outliers skew the data set

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Cerebral Blood Flow Changes

- Increased CBF reflects increased cerebral demand
  - Inflammatory, metabolic, ischemic
- Suggests that hypoxic hypobaric exposure induces transient WM damage
  - Need for adequate recovery time between exposures? 72 h?
  - Effect of hypoxia alone (ROBD) on these changes still under investigation by our team
- Underlying physiological explanation remains unclear
- Next project:
  - 3 limbs, all same subjects (n = 40)
  - Will include ROBD, nonhypoxic hypobaric, and hypoxic hypobaric exposures
  - Baseline MRI, MRI immediately after exposure, MRI at 72-96h
  - TCD during exposure; physiologic monitoring; neurocognitive testing

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.

Questions?

Courtesy of Dr. Paul Sherman

Cleared, AFIMSC/PA, Case # 2018-0296, 1 Oct 2018.