



DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS



15 MAR 2017

MEMORANDUM FOR SGVT
ATTN: CAPT MICHAEL HOSSACK

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **A Proposed Mechanism of Neuronal Injury in Pilots & Aircrew Personnel with Hypobaric Exposure** presented at/published to **American Academy of Neurology, Boston, MA, 22-28 April 2017** in accordance with MDWI 41-108, has been approved and assigned local file #**17135**.
2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.
3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are a 59 MDW staff member, we can forward your request for funds to the designated Wing POC at the Chief Scientist's Office, Ms. Alice Houy, office phone: 210-292-8029; email address: alice.houy.civ@mail.mil.
4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

INSTRUCTIONS

USE ONLY THE MOST CURRENT 59 MDW FORM 3039 LOCATED ON AF E-PUBLISHING

1. The author must complete page two of this form:
 - a. In Section 2, add the funding source for your study [e.g., 59 MDW CRD Graduate Health Sciences Education (GHSE) (SG5 O&M); SG5 R&D; Tri-Service Nursing Research Program (TSNRP); Defense Medical Research & Development Program (DMRDP); NIH; Congressionally Directed Medical Research Program (CDMRP) ; Grants; etc.]
 - b. In Section 2, there may be funding available for journal costs, if your department is not paying for figures, tables or photographs for your publication. Please state "YES" or "NO" in Section 2 of the form, if you need publication funding support.
2. Print your name, rank/grade, sign and date the form in the author's signature block or use an electronic signature.
3. Attach a copy of the 59 MDW IRB or IACUC approval letter for the research related study. If this is a technical publication/presentation, state the type (e.g. case report, QA/QI study, program evaluation study, informational report/briefing, etc.) in the "Protocol Title" box.
4. Attach a copy of your abstract, paper, poster and other supporting documentation.
5. Save and forward, via email, the processing form and all supporting documentation to your unit commander, program director or immediate supervisor for review/approval.
6. On page 2, have either your unit commander, program director or immediate supervisor:
 - a. Print their name, rank/grade, title; sign and date the form in the approving authority's signature block or use an electronic signature.
7. Submit your completed form and all supporting documentation to the CRD for processing (59crdpubspres@us.af.mil). **This should be accomplished no later than 30 days before final clearance is required to publish/present your materials.** If you have any questions or concerns, please contact the 59 CRD/Publications and Presentations Section at 292-7141 for assistance.
8. The 59 CRD/Publications and Presentations Section will route the request form to clinical investigations, 502 ISG/JAC (Ethics Review) and Public Affairs (59 MDW/PA) for review and then forward you a final letter of approval or disapproval.
9. Once your manuscript, poster or presentation has been approved for a one-time public release, you may proceed with your publication or presentation submission activities, as stated on this form. **Note:** For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.
10. If your manuscript is accepted for scientific publication, please contact the 59 CRD/Publications and Presentations Section at 292-7141. This information is reported to the 59 MDW/CC. All medical research or technical information publications/presentations must be reported to the Defense Technical Information Center (DITC). See 59 MDWI 41-108, *Presentation and Publication of Medical and Technical Papers*, for additional information.
11. The Joint Ethics Regulation (JER) DoD 5500.07-R, *Standards of Conduct*, provides standards of ethical conduct for all DoD personnel and their interactions with other non-DoD entities, organizations, societies, conferences, etc. Part of the Form 3039 review and approval process includes a legal ethics review to address any potential conflicts related to DoD personnel participating in non-DoD sponsored conferences, professional meetings, publication/presentation disclosures to domestic and foreign audiences, DoD personnel accepting non-DoD contributions, awards, honoraria, gifts, etc. The specific circumstances for your presentation will determine whether a legal review is necessary. **If you (as the author) or your supervisor check "NO" in block 17 of the Form 3039, your research or technical documents will not be forwarded to the 502 ISG/JAC legal office for an ethics review.** To assist you in making this decision about whether to request a legal review, the following examples are provided as a guideline:

For presentations before professional societies and like organizations, the 59 MDW Public Affairs Office (PAO) will provide the needed review to ensure proper disclaimers are included and the subject matter of the presentation does not create any cause for DoD concern.

If the sponsor of a conference or meeting is a DoD entity, an ethics review of your presentation is not required, since the DoD entity is responsible to obtain all approvals for the event.

If the sponsor of a conference or meeting is a non-DoD commercial entity or an entity seeking to do business with the government, then your presentation should have an ethics review.

If your travel is being paid for (in whole or in part) by a non-Federal entity (someone other than the government), a legal ethics review is needed. These requests for legal review should come through the 59 MDW Gifts and Grants Office to 502 ISG/JAC.

If you are receiving an honorarium or payment for speaking, a legal ethics review is required.

If you (as the author) or your supervisor check "YES" in block 17 of the Form 3039, your research or technical documents will be forwarded simultaneously to the 502 ISG/JAC legal office and PAO for review to help reduce turn-around time. If you have any questions regarding legal reviews, please contact the legal office at (210) 671-5795/3365, DSN 473.

NOTE: All abstracts, papers, posters, etc., should contain the following disclaimer statement:

"The views expressed are those of the [author(s)] [presenter(s)] and do not reflect the official views or policy of the Department of Defense or its Components"

NOTE: All abstracts, papers, posters, etc., should contain the following disclaimer statement for research involving humans:

"The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402."

NOTE: All abstracts, papers, posters, etc., should contain the following disclaimer statement for research involving animals, as required by AFMAN 40-401_IP :

"The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966, as amended."

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1. TO: CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol) Michael Hossack, Capt, O-3, Neuro	3. GME/GHSE STUDENT: <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	4. PROTOCOL NUMBER: FWH20140087H
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5. PROTOCOL TITLE: (**NOTE:** For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.)
MRI Following Single Exposure to Hypobaric and/or Hypoxia

6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:
A Proposed Mechanism of Neuronal Injury in Pilots & Aircrew Personnel with Hypobaric Exposure

7. FUNDING RECEIVED FOR THIS STUDY? YES NO FUNDING SOURCE: AF SG

8. DO YOU NEED FUNDING SUPPORT FOR PUBLICATION PURPOSES: YES NO

9. IS THIS MATERIAL CLASSIFIED? YES NO

10. IS THIS MATERIAL SUBJECT TO ANY LEGAL RESTRICTIONS FOR PUBLICATION OR PRESENTATION THROUGH A COLLABORATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA), MATERIAL TRANSFER AGREEMENT (MTA), INTELLECTUAL PROPERTY RIGHTS AGREEMENT ETC.?
 YES NO **NOTE:** If the answer is YES then attach a copy of the Agreement to the Publications/Presentations Request Form.

11. MATERIAL IS FOR: DOMESTIC RELEASE FOREIGN RELEASE
CHECK APPROPRIATE BOX OR BOXES FOR APPROVAL WITH THIS REQUEST. ATTACH COPY OF MATERIAL TO BE PUBLISHED/PRESENTED.

11a. PUBLICATION/JOURNAL (List intended publication/journal.)

11b. PUBLISHED ABSTRACT (List intended journal.)

11c. POSTER (To be demonstrated at meeting: name of meeting, city, state, and date of meeting.)

11d. PLATFORM PRESENTATION (At civilian institutions: name of meeting, state, and date of meeting.)
American Academy of Neurology, Boston MA, April 22-28, 2017

11e. OTHER (Describe: name of meeting, city, state, and date of meeting.)

12. HAVE YOUR ATTACHED RESEARCH/TECHNICAL MATERIALS BEEN PREVIOUSLY APPROVED TO BE PUBLISHED/PRESENTED?
 YES NO ASSIGNED FILE # 2017-0330 88PA DATE 30 Jan 17

13. EXPECTED DATE WHEN YOU WILL NEED THE CRD TO SUBMIT YOUR CLEARED PRESENTATION/PUBLICATION TO DTIC
NOTE: All publications/presentations are required to be placed in the Defense Technical Information Center (DTIC).

DATE March 14, 2017	
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14. 59 MDW PRIMARY POINT OF CONTACT (Last Name, First Name, M.I., email) Hossack, Michael R.; michael.r.hossack.mil@mail.mil	15. DUTY PHONE/PAGER NUMBER (210) 916-2203/(210) 513-1568
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16. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.			
LAST NAME, FIRST NAME AND M.I.	GRADE/RANK	SQUADRON/GROUP/OFFICE SYMBOL	INSTITUTION (If not 59 MDW)
a. Primary/Corresponding Author Hossack, Michael	Capt/O-3	959 CSPS/SGVT	
b. Sladky, John H.	Col/O-6	959 MDOS/SGOT	
c. McGuire, Stephen A.	CTR	USAF School of Aerospace Medicine	Aeromedical Research Dept.
d.			
e.			

17. IS A 502 ISG/JAC ETHICS REVIEW REQUIRED (JER DOD 5500.07-R)? YES NO

I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401_IP, AND 59 MDWI 41-108. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.

18. AUTHOR'S PRINTED NAME, RANK, GRADE Hossack, Michael R Capt USAF, O-3	19. AUTHOR'S SIGNATURE HOSSACK MICHAEL R. 1029324758	20. DATE 28 Feb 2017
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21. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE Sladky, John H Lt Col USAF, O-5	22. APPROVING AUTHORITY'S SIGNATURE SLADKY JOHN HWA. 1099007237	23. DATE 1 March 2017
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PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1st ENDORSEMENT (59 MDW/SGVU Use Only)

TO: Clinical Research Division 59 MDW/CRD Contact 292-7141 for email instructions.	24. DATE RECEIVED March 06, 2017	25. ASSIGNED PROCESSING REQUEST FILE NUMBER 17135
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26. DATE REVIEWED March 10, 2017	27. DATE FORWARDED TO 502 ISG/JAC
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28. AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES: NO YES If yes, give date. _____ N/A

29. COMMENTS APPROVED DISAPPROVED
Abstract for IRB approved study with appropriate disclaimers. Approved

30. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER Kevin Kupferer/GS13/Human Research Subject Protection Expert	31. REVIEWER SIGNATURE KUPFERER KEVIN R. 1086667270 <small>Digitally signed by KUPFERER KEVIN R. 1086667270 DN: cn=KUPFERER KEVIN R. 1086667270, o=59 MDW/CRD, ou=59 MDW/CRD, email=KUPFERER KEVIN R. 1086667270 Date: 2017.03.10 14:31:08 -0500</small>	32. DATE March 10, 2017
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2nd ENDORSEMENT (502 ISG/JAC Use Only)

33. DATE RECEIVED	34. DATE FORWARDED TO 59 MDW/PA
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35. COMMENTS APPROVED (In compliance with security and policy review directives.) DISAPPROVED

36. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	37. REVIEWER SIGNATURE	38. DATE
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3rd ENDORSEMENT (59 MDW/PA Use Only)

39. DATE RECEIVED March 14, 2017	40. DATE FORWARDED TO 59 MDW/SGVU March 15, 2017
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41. COMMENTS APPROVED (In compliance with security and policy review directives.) DISAPPROVED

42. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER Kevin Inuma, SSgt/E-5, 59 MDW Public Affairs	43. REVIEWER SIGNATURE IINUMA KEVIN MITSUGU. 1296227 613 <small>Digitally signed by IINUMA KEVIN MITSUGU. 1296227613 DN: cn=IINUMA KEVIN MITSUGU. 1296227613, o=59 MDW/PA, ou=59 MDW/PA, email=IINUMA KEVIN MITSUGU. 1296227613 Date: 2017.03.15 08:04:30 -0500</small>	44. DATE March 15, 2017
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4th ENDORSEMENT (59 MDW/SGVU Use Only)

45. DATE RECEIVED	46. SENIOR AUTHOR NOTIFIED BY PHONE OF APPROVAL OR DISAPPROVAL <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> COULD NOT BE REACHED <input type="checkbox"/> LEFT MESSAGE
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47. COMMENTS APPROVED DISAPPROVED

48. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	49. REVIEWER SIGNATURE	50. DATE
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A Proposed Mechanism of Neuronal Injury in Pilots & Aircrew Personnel with Hypobaric Exposure

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Integrity ★ Service ★ Excellence



Disclaimer



- ✧ The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the U.S. Government.
- ✧ Research is sponsored by USAF/SG, 711HPW, 59MDW, and JPC-5.



Background: U-2 Pilots & White Matter Hyperintensities (WMH)



- U-2 pilots display an increased incidence of white-matter hyperintensities (WMH) on MRI compared to healthy age-matched controls (non-pilots)
- U-2 pilots demonstrate reduced neurocognitive performance associated with burden of WMH
- WMH are a marker of cerebral integrity and associated with cognitive decline





Background: Aircrew & WMH



- Similar findings of increased WMH have been replicated in aircrew personnel with non-hypoxic hypobaric exposure via altitude chamber training
- Aircrew personnel undergo training per standard USAF procedure in altitude chambers that simulate conditions at 25,000 feet
- Sessions are 30 minutes long and 100% oxygen is provided continuously via chamber masks
- Occupational exposure to non-hypoxic, hypobaric conditions is associated with the number of sub-cortical WMHs



USAF photo by Joel Martinez.



Goals of Ongoing Studies



- What is the mechanism of WMH formation in non-hypoxic hypobaria?
 - Microemboli, breakdown of BBB, neuroinflammation?
- Is there a specific pattern of cellular injury?
 - Cyto-architectural changes, metabolic changes?
 - Glial cells, neuronal cells, axons?
- Are there measurable changes in the brain prior to WMH formation?
 - How early after exposure can changes be detected?



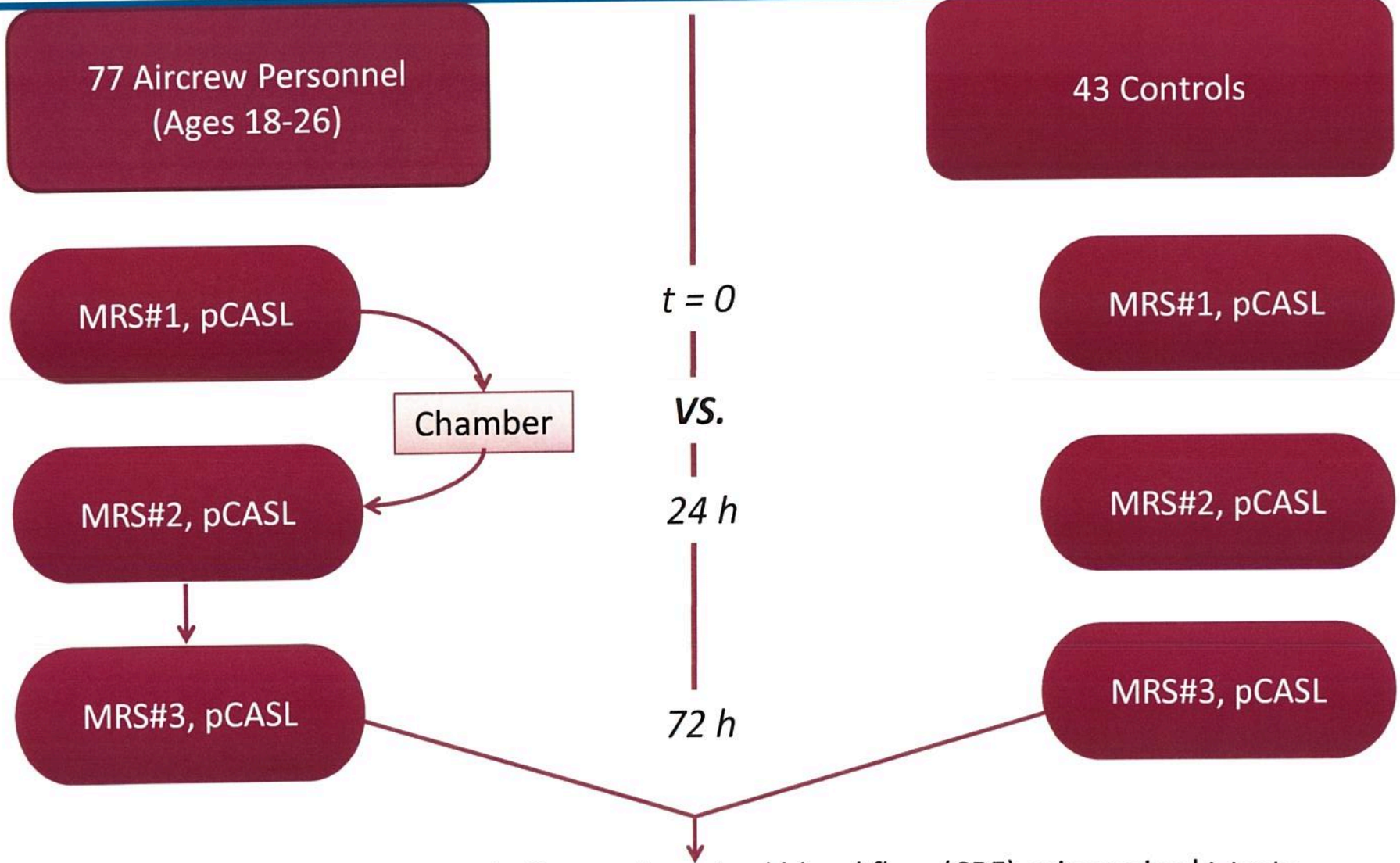
Study Design



- Use non-invasive neuroimaging techniques – MR spectroscopy (MRS) and arterial spin labeling (ASL) – to look for any acute changes occurring at the neuronal level in subjects exposed to non-hypoxic hypobaric conditions
- 77 USAF aircrew personnel underwent non-hypoxic, hypobaric exposure (per AF standard protocol)
- MRS (3 Tesla) performed prior to 1st lifetime exposure and repeated 24 and 72 hours after exposure
- Pseudocontinuous ASL (pCASL) was performed in a similar fashion
- MRS and pCASL imagings from 77 cases were compared to MRS and pCASL results in 43 healthy, age-matched controls



Study Algorithm



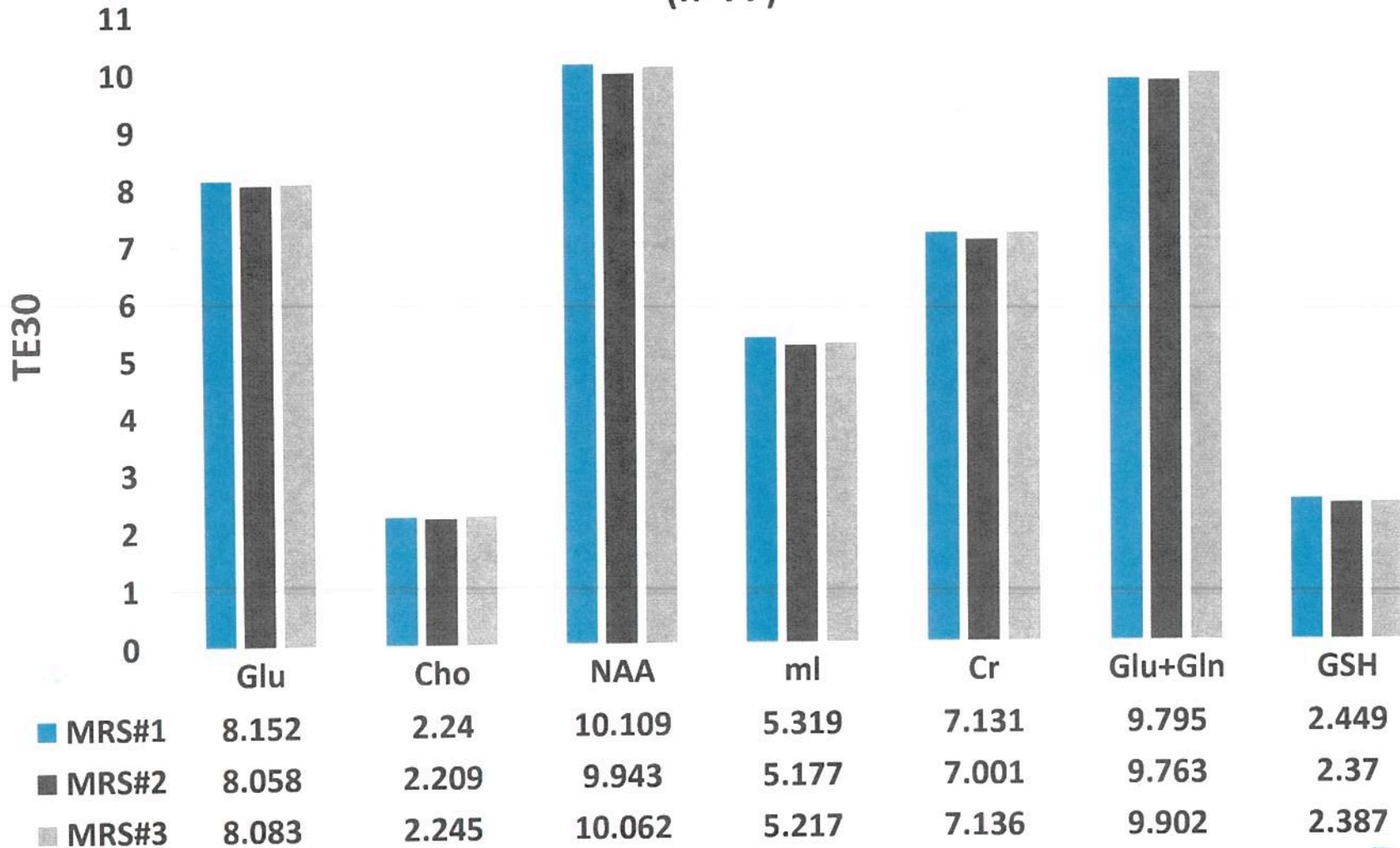
Comparison of proton metabolites and cerebral blood flow (CBF) using paired t-tests



Results: MR Spectroscopy



AFC TE30 Average
(n=77)





Results: MR Spectroscopy



*Average of metabolite peaks measured over both frontal lobes
using multi-voxel analysis*

	Glu	Cho	NAA	ml	Cr	Glu+Gln	GSH
MRS#1	8.152	2.24	10.109	5.319	7.131	9.795	2.449
MRS#2	8.058	2.209	9.943	5.177	7.001	9.763	2.37
MRS#3	8.083	2.245	10.062	5.217	7.136	9.902	2.387

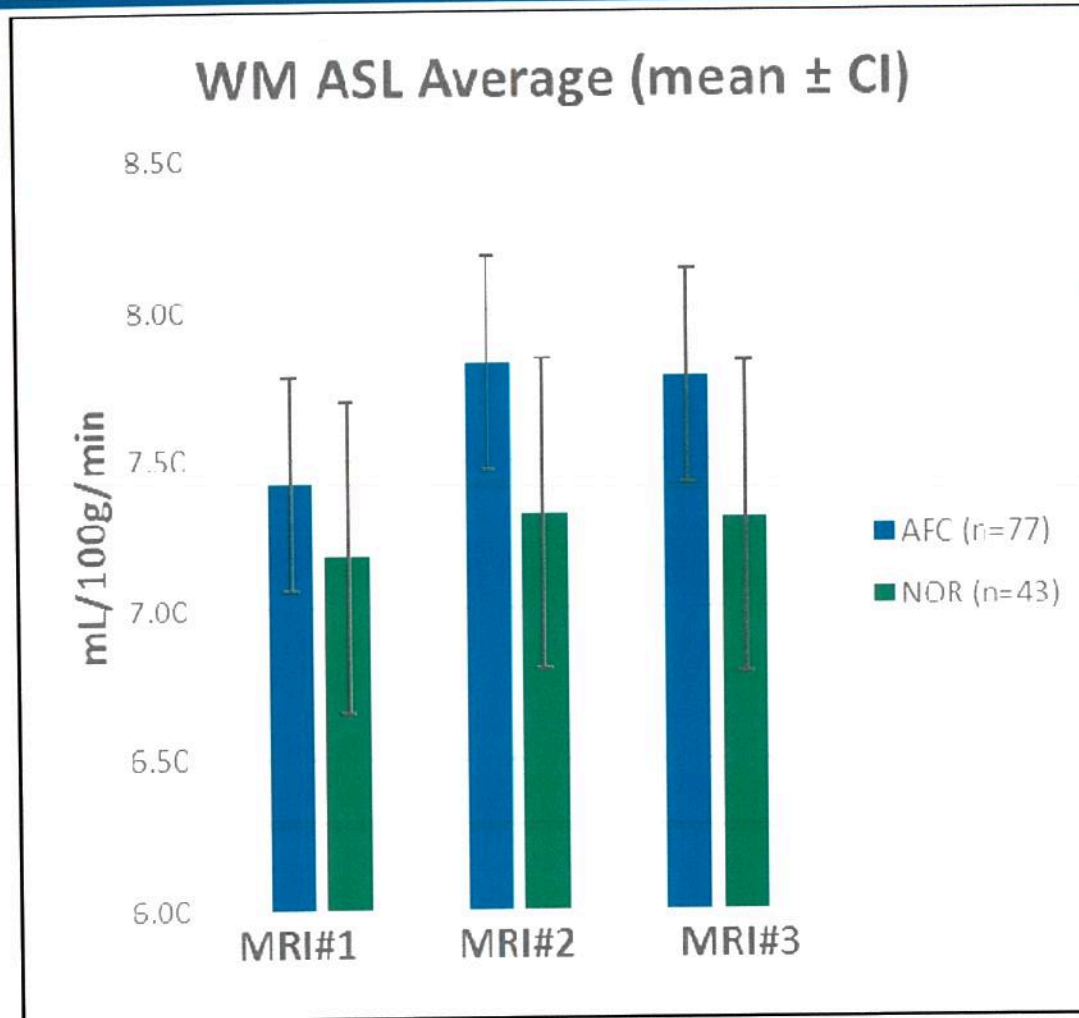
AFC paired t-test p-value

#1-#2	0.403	0.147	0.066	0.028	0.103	0.983	0.126
#1-#3	0.423	0.803	0.6	0.241	0.908	0.293	0.372
#2-#3	0.877	0.165	0.311	0.597	0.099	0.312	0.707

Key: #1 = pre-exposure, #2 = post 24 h, #3 = post 72 h



Results: Arterial Spin Labeling



Key: #1 = pre-exposure, #2 = post 24 h, #3 = post 72 h



Conclusions



- Exposed subjects had a decrease at T+24 in myo-inositol ($p=0.028$), NAA ($p=0.066$), Cr ($p=0.076$), and GSH ($p=0.063$) with no significant change in controls
- Decreased NAA and myo-inositol indicate compromised integrity of neuronal and glial cells, respectively
- pCASL showed an upregulation of both white and gray matter CBF at both T+24 and T+72 hours in the exposed subjects with no significant change in the controls (subjects WM $p=0.004/0.021$; GM $0.065/0.037$)
- Changes in CBF occurred first in WM areas followed by gray matter areas



Conclusions



- Hypobaric exposure without hypoxia results in oxidative stress to neurons and glial cells and can be detected using non-invasive neuroimaging within 24 hours of exposure
- Increases in CBF likely occur secondary to neuronal oxidative stress
- Metabolite peaks trended toward baseline levels at 72 hours, implying a healing process is likely involved early after hypobaric exposure
- WMH found in pilots and aircrew personnel are likely a function of both the frequency and cumulative effects of oxidative stress secondary to hypobaric exposure



Bibliography



Chang L, Munsaka SM, Kraft-Terry S, et al. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. *J Neuroimmune Pharmacol.* 2013; 8(3):576-593.

Galluzzi S, Lanni C, Pantoni L, et al. White matter lesions in the elderly: pathophysiological hypothesis on the effect on brain plasticity and reserve. *J Neurol Sci.* 2008; 273(1-2):3-9.

Kochunov P, Robin DA, Royall DR, et al. Can structural MRI indices of cerebral integrity track cognitive trends in executive control function during normal maturation and adulthood? *Hum Brain Mapp.* 2009; 30(8):2581-2594.

Kochunov P, Thompson PM, Coyle TR, et al. Relationship among neuroimaging indices of cerebral health during normal aging. *Hum Brain Mapp.* 2008; 29(1):36-45.

McGuire S, Sherman P, Profenna L, et al. White matter hyperintensities on MRI in high-altitude U-2 pilots. *Neurology.* 2013; 81(8):729-735.

McGuire SA, Sherman PM, Wijtenburg SA, et al. White matter hyperintensities and hypobaric exposure. *Ann Neurol.* 2014; 76(5):719-726.

McGuire SA, Tate DF, Wood J, et al. Lower neurocognitive function in high-altitude U-2 pilots: Relationship to white matter hyperintensities. *Neurology.* 2014; 83(7):638-645.