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

16 MAR 2017

MEMORANDUM FOR SGVT
ATTN: CAPT PHILIPPINE DANA PERALTA

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **A Proposed Mechanism for Hypobaria-Induced Neuronal Injury: A Swine Model** presented at/published to **2017 AAN (American Academy of Neurology) Annual Meeting, Boston, MA, 22-28 April 2017** in accordance with MDWI 41-108, has been approved and assigned local file #**17142.**

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)	3. GME/GHSE STUDENT:	4. PROTOCOL NUMBER:
	Philippine Dana Peralta, Capt, O-3, 59 MDW	☒ YES ☐ NO	FWH20160011A

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.)

Brain MRI and serological effects of hypobaric exposure to 30,000 ft and hyperoxemic exposure at sea level in a sus scrofa domestica model

6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:

A Proposed Mechanism for Hypobaria-Induced Neuronal Injury: A Swine Model

7. FUNDING RECEIVED FOR THIS STUDY? ☒ YES ☐ NO FUNDING SOURCE: USAF/SG, JPC-5

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.)
2017 AAN (American Academy of Neurology) Annual Meeting, Boston, MA, 22-28 April 2017

☐ 11d. PLATFORM PRESENTATION (At civilian institutions: name of meeting, state, and date of meting.)

☐ 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 # 88ABW-2017-0583 DATE 10 Feb 2017

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
10 Mar 2017

14. 59 MDW PRIMARY POINT OF CONTACT (Last Name, First Name, M.I., email)	15. DUTY PHONE/PAGER NUMBER
Middleton, Deborah; deborah.middleton.ctr@us.af.mil	210.292.0494

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 Peralta, Philippine Dana D	Capt, O-3	959 CSPS/SGVT	SAMMC
b. Sladky, John H	LtCol, 0-5	959 MDOS/SGOT	SAMMC
c. Sherman, Paul	Col, 0-6	59 MDW	
d. McGuire, Stephen A	(Ret) Col, 0-6	59 MDW	
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	19. AUTHOR'S SIGNATURE	20. DATE
P. Dana Peralta, Capt, O-3	PERALTA.PHILIPPINE.DANA.1385168205	03/02/2017
21. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE	**22. APPROVING AUTHORITY'S SIGNATURE**	**23. DATE**
John H. Sladky, LtCol, O-5; Program Director, SAMMC Neurology	SLADKY.JOHN.HWA.1099007237	03/03/2017

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 09, 2017	25. ASSIGNED PROCESSING REQUEST FILE NUMBER 17142
26. DATE REVIEWED		27. DATE FORWARDED TO 502 ISG/JAC

28. AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES: ☐ NO ☒ YES If yes, give date. 13 March 2017 ☐ N/A

29. COMMENTS ☒ APPROVED ☐ DISAPPROVED

30. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	31. REVIEWER SIGNATURE	32. DATE
Linda D Harris, GS-14, Chief, Ops Branch	HARRIS.LINDA.DAWN.113189058 0	March 15, 2017

2nd ENDORSEMENT (502 ISG/JAC Use Only)

33. DATE RECEIVED	34. DATE FORWARDED TO 59 MDW/PA

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

3rd ENDORSEMENT (59 MDW/PA Use Only)

39. DATE RECEIVED	40. DATE FORWARDED TO 59 MDW/SGVU
March 15, 2017	March 15, 2017

41. COMMENTS ☒ APPROVED (In compliance with security and policy review directives.) ☐ DISAPPROVED

42. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	43. REVIEWER SIGNATURE	44. DATE
Kevin Iinuma, SSgt/E-5, 59 MDW Public Affairs	IINUMA.KEVIN.MITSUGU.1296227 613	March 15, 2017

4th ENDORSEMENT (59 MDW/SGVU Use Only)

45. DATE RECEIVED	46. SENIOR AUTHOR NOTIFIED BY PHONE OF APPROVAL OR DISAPPROVAL ☐ YES ☐ NO ☐ COULD NOT BE REACHED ☐ LEFT MESSAGE

47. COMMENTS ☐ APPROVED ☐ DISAPPROVED

48. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	49. REVIEWER SIGNATURE	50. DATE

A PROPOSED MECHANISM FOR HYPOBARIA-INDUCED NEURONAL INJURY: A SWINE MODEL

P. Dana Peralta[1]; John H. Sladky[1]; Paul Sherman[1,2]; Stephen A. McGuire[1,2]

[1]Neurology Department, San Antonio Military Medical Center, Fort Sam Houston, TX; [2]U.S. Air Force School of Aerospace Medicine, Aeromedical Research Department, Wright-Patterson AFB, OH

BACKGROUND

Non-hypoxic hypobaric exposure in Air Force U-2 pilots and hypobaric chamber personnel is associated with increased brain white matter hyperintensities (WMH) and decrements in neurocognitive processing. The mechanism for this is unknown. We hypothesized that if injury is due to diffuse axonal degradation, this would manifest as changes in unrestricted water diffusion and be demonstrable through diffusion magnetic resonance imaging (MRI), utilizing advanced techniques such as multi-b-value diffusion (Q-space) and kurtosis anisotropy. We developed a swine model to test this theory.

PROTOCOL OVERVIEW

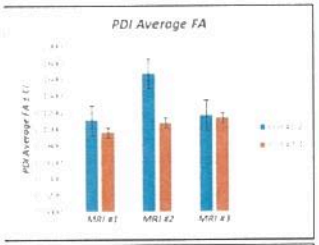
Day 1:	**Baseline MRI**
Day 6-21:	**Hypobaric Chamber Exposure Flights** • Each subject 6 flights over 3 weeks (1 flight q3days) **Subjects** • Hypobaric Group (n=12) to 30,000 feet, 100% FiO2 • Control Group (n=12) to 5,000 feet, 21% FiO2
Day 22:	**Post-flight MRI**
Day 51:	**Final 4-week post-flight MRI**

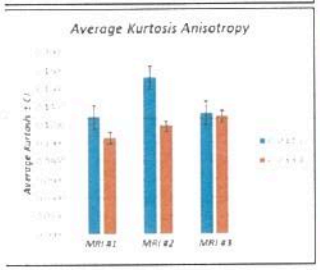
METHODS

Subjects: 24 female miniature pigs (Sus scrofa domestica).
Exposure: 12 repetitively exposed to non-hypoxic hypobaria at 30,000 feet; 12 were controls exposed to standard cabin pressures of 5,000 feet on ambient air.
All subjects imaged 3 times – at baseline, post-flight day 22, and day 51.
Analysis: 2-tailed t-tests were used for individual and group comparisons of perfusion diffusion index (PDI) and kurtosis, as well as an age-adjusted average fractional anisotropy.

RESULTS

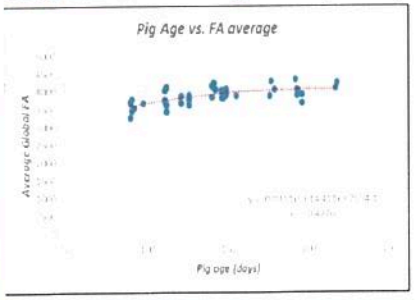
PDI and mean kurtosis anisotropy revealed an increase in unrestricted water diffusion immediately after repetitive high-altitude exposures. Repeat imaging 4 weeks post-exposure showed normalization to pre-exposure values.

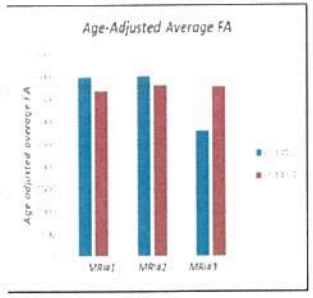




By 59MDW

Age-adjusted mean fractional anisotropy (FA) at 4 weeks post-exposure was significantly decreased in the high-altitude group when compared to controls ($p < 0.001/0.547$).





CONCLUSION

Our study demonstrates increase in unrestricted free water immediately after repetitive high-altitude exposure that is consistent with injury, not seen in the control group. The significant decrease in FA at 4 weeks further supports that degradation of axonal injury occurred and replicates similar MRI findings in humans. This study provides evidence that repetitive hypobaric exposure incites axonal damage. Moreover, it supports the utility of advanced diffusion imaging techniques such as kurtosis anisotropy, which may more accurately reflect the heterogeneous reality of non-Gaussian diffusion. Our study is the first, to our knowledge, to provide evidence that repetitive non-hypoxic hypobaric exposure incites axonal damage, as well as demonstrates our swine model as a feasible vector by which to study hypobaric neuronal injury and, possibly, other axonal injury processes like TBI.

By 59MDW

BIBLIOGRAPHY

Alexander DC, Hubbard PL, Hall MG, Moore EA, Ptito M, et al. Orientationally invariant indices of axon diameter and density from diffusion MRI. Neuroimage. 2011; 52(4):1374-1389.

Connolly D, Lee V. Odds ratio meta analysis and increased prevalence of white matter injury in healthy divers. Aerosp Med Hum Perform. 2015; 86(1):928-935.

Hou D, Tong KA, Ashwal S, Oyoyo U, Obenaus A, et al. Diffusion weighted magnetic resonance imaging improves outcome prediction in adult traumatic brain injury. J Neurotrauma. 2007; 24(10):1558-1569.

Kochunov P, Chiappelli J, Hong LE. Permeability diffusivity modeling yet fractional anisotropy on white matter integrity assessment and application in schizophrenia. Neuroimage Clin. 2013; 3:18-26.

McGuire SA, Sherman PM, Brown AC, Robinson AP, Tate DF, et al. Hyperintense white matter lesions in 50 high-altitude pilots with neurologic decompression sickness. Aviat Space Environ Med. 2012; 83(12):1117-1122.

McGuire S, Sherman P, Pinderna I, Grogan P, Sladky J, 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, Rowland LM, Grogan PM, et al. White matter hyperintensities and hypobaric exposure. Ann Neurol. 2014; 76(5):719-726.

McGuire SA, Tate DF, Wood J, Sladky Jr, McDonald B, et al. Lower neurocognitive function in U-2 pilots: relationship to white matter hyperintensities. Neurology. 2014; 83(7):638-645.

Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. J Head Trauma Rehabil. 2003; 18(4):307-316.

Steven AJ, Zhuo J, Melhem ER. Diffusion kurtosis imaging: an emerging technique for evaluating the microstructural environment of the brain. Neuroradiology and Neck Imaging. AJR Am J Roentgenol. 2014; 202(1):W26-W33.