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14. ABSTRACT The purpose of this study was to demonstrate that U-2 pilot occupational exposure to hypobarica leads to increased incidence of white matter hyperintensities (WMH) with a more uniform distribution throughout the brain irrespective of clinical neurologic decompression sickness history. We evaluated imaging findings in 102 U-2 pilots and 91 controls matched for age, health, and education levels. Three-dimensional, T2-weighted, high-resolution (1-mm isotropic) imaging data were collected using fluid-attenuated inversion recovery sequence on a 3-tesla magnetic resonance imaging scanner. Whole-brain and regional WMH volume and number were compared between groups using a 2-tailed Wilcoxon rank sum test. U-2 pilots demonstrated an increase in volume (394%; p = 0.004) and number (295%; p < 0.001) of WMH. Analysis of regional distribution demonstrated WMH more uniformly distributed throughout the brain in U-2 pilots compared with mainly frontal distribution in controls. Pilots with occupational exposure to hypobarica showed a significant increase in WMH lesion volume and number. Unlike the healthy controls with predominantly WMH in the frontal white matter, WMH in pilots were more uniformly distributed throughout the brain. This is consistent with our hypothesized pattern of damage produced by interaction between microemboli and cerebral tissue, leading to thrombosis, coagulation, inflammation, and/or activation of innate immune response, although further studies will be necessary to clarify the pathologic mechanisms responsible.					
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White matter hyperintensities on MRI in high-altitude U-2 pilots

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White matter hyperintensities on MRI in high-altitude U-2 pilots

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ABSTRACT

Objective: To demonstrate that U-2 pilot occupational exposure to hypobaria leads to increased incidence of white matter hyperintensities (WMH) with a more uniform distribution throughout the brain irrespective of clinical neurologic decompression sickness history.

Methods: We evaluated imaging findings in 102 U-2 pilots and 91 controls matched for age, health, and education levels. Three-dimensional, T2-weighted, high-resolution (1-mm isotropic) imaging data were collected using fluid-attenuated inversion recovery sequence on a 3-tesla MRI scanner. Whole-brain and regional WMH volume and number were compared between groups using a 2-tailed Wilcoxon rank sum test.

Results: U-2 pilots demonstrated an increase in volume (394%; $p = 0.004$) and number (295%; $p < 0.001$) of WMH. Analysis of regional distribution demonstrated WMH more uniformly distributed throughout the brain in U-2 pilots compared with mainly frontal distribution in controls.

Conclusion: Pilots with occupational exposure to hypobaria showed a significant increase in WMH lesion volume and number. Unlike the healthy controls with predominantly WMH in the frontal white matter, WMH in pilots were more uniformly distributed throughout the brain. This is consistent with our hypothesized pattern of damage produced by interaction between microemboli and cerebral tissue, leading to thrombosis, coagulation, inflammation, and/or activation of innate immune response, although further studies will be necessary to clarify the pathologic mechanisms responsible. *Neurology*® 2013;81:729-735

GLOSSARY

BET = brain extraction tool; **DCS** = decompression sickness; **FLAIR** = fluid-attenuated inversion recovery; **FMRIB** = Functional MRI of the Brain; **NDCS** = neurologic decompression sickness; **RF** = radiofrequency; **3D** = 3-dimensional; **USAF** = United States Air Force; **WMH** = white matter hyperintensities.

The United States Air Force (USAF) operates the U-2 high-altitude reconnaissance aircraft, which maintains a cabin altitude of approximately 9,000 m (28,000–30,000 ft) while operating above 21,000 m.¹ Decompression sickness (DCS), including CNS neurologic DCS (NDCS), is a known occupational risk from exposure to low ambient pressure (hypobaria) in high-altitude aviators.² The risk of DCS per flight increased from 0.076% pre-2006 to 0.23% during the 2006–2010 operation years, believed to be related to more frequent and longer periods of exposure for the pilots.^{3,4} Importantly, 44% of episodes were diagnosed as NDCS, with symptoms ranging from mild, such as complaints of slowed thought processes, to severe, including anomia, confusion, unresponsiveness,⁵ and permanent cognitive decline.⁶

We previously reported that clinical NDCS was associated with an increase in white matter hyperintensities (WMH).⁷ Herein, we examine the volume, number, and regional distribution of subcortical WMH in a healthy, young population of age-, health-, and education-matched pilots and controls who lack the common risk factors for recognized WMH etiologies, leaving occupational exposure to hypobaria as the main intergroup contrast. We hypothesized that this

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increase in WMH was directly or indirectly related to microbubbles of predominantly nitrogen gas formed during hypobaria. Specifically, we hypothesized the entire U-2 pilot population would exhibit significantly greater subcortical WMH volume and number with a more uniform regional distribution throughout the brain than a normative control group.

METHODS Standard protocol approvals, registrations, and patient consents. This study was reviewed and approved by the Air Force Research Laboratory Institutional Review Board. All study subjects were active duty members of the US Armed Forces. All participants were recruited with strict adherence to Department of Defense requirements regarding protection of human subjects' research. Participation in this study was voluntary without commander involvement or knowledge. All participants acknowledged this was not an anonymous study and results would become a permanent part of their electronic military medical record and provided informed consent.

All high-altitude U-2 pilots currently on active duty in the USAF were invited to participate, with a participation rate exceeding 90%. All active-duty military members with a doctorate degree assigned to duty within the continental United States were eligible to participate as normal controls, although recruitment was predominantly from the 2 San Antonio graduate medical education military facilities through presentations at professional staff meetings. Additionally, presentations were made seeking volunteers at international aerospace meetings and through electronic messaging such as facility daily bulletins. All pilots were healthy at the time of testing, meeting USAF Flying Class II standards⁸ and on active USAF flying status. All normative subjects also met USAF Flying Class II neurologic standards. Military medical records were reviewed to confirm self-reported medical information. Briefly, exclusionary criteria included a history of any of the following: head trauma with any loss of consciousness or amnesia; migraine headache; psychiatric or psychological disease requiring any medication or hospitalization; hypertension requiring more than a single angiotensin-converting enzyme inhibitor for control; hyperlipidemia requiring more than a single statin for control; diabetes or glucose intolerance; any neurologic disease including infection, seizure, or stroke; familial degenerative neurologic disease; substance or drug abuse or dependence; or any systemic disease with the potential for neurologic involvement. All subjects were between the ages of 26 and 50 years (37.0 ± 6.0 years, range 28–50 years, and age 36.0 ± 6.2 years, range 26–50 years, for pilots and controls, respectively, $p = 0.063$). Both sexes were included. All subjects were evaluated between May 2011 and December 2012. Subjects did not receive compensation for participation in this study, but subjects' travel costs were reimbursed as permitted under federal government travel regulations.

Imaging. Structural MRI data for the pilots were collected at the Research Imaging Institute, University of Texas Health Science Center, San Antonio, using a Siemens 3T Tim Trio scanner (Siemens AG, Erlangen, Germany) equipped with a 12-channel phase array coil. Structural MRI data for the normative doctorate-degree subjects were collected at Wilford Hall Ambulatory Surgical Clinic, 59th Medical Wing, Lackland AFB, TX, using a Siemens 3T Verio scanner equipped with a 32-channel phase array coil. Both scanners were operated under quality control and assurance guidelines in accordance with recommendations by the American College of Radiology and utilized the same imaging sequence.

T2-weighted, 3-dimensional (3D), high-resolution (isotropic 1-mm), fluid-attenuated inversion recovery (FLAIR) data were collected using a turbo-spin sequence with the following parameters: repetition time/echo time/inversion time/flip angle/echo train length = 5 seconds/353 milliseconds/1.8 seconds/180°/221. This 3D FLAIR protocol was specifically designed to overcome the limitations of a 2-dimensional thick-slice (5- to 10-mm) clinical imaging protocol and to permit increased detection of smaller lesions with accurate tracing of lesion boundaries.^{9,10} This 3D FLAIR sequence uses a nonselective inversion radiofrequency (RF) pulse to suppress CSF pulsation artifacts to reduce false-negative hyperintense artifacts seen near CSF-containing structures in the 2-dimensional FLAIR sequences.¹¹

In addition to FLAIR data, high-resolution (isotropic 0.8 mm, voxel size = 0.5 mm^3) T1-weighted data were collected with the following sequence parameters: echo time/repetition time/inversion time = 3.04/2,100/785 milliseconds, flip angle = 11°. A retrospective motion-correction technique¹² was used to reduce subject motion-related artifacts. Magnetic resonance spectroscopy, arterial spin labeling, and diffusion tensor imaging data were collected but not included in this report.

A cross-calibration protocol was performed to calculate linear scaling coefficients for the volume and number of subcortical WMH. Under this protocol, 11 subjects with variable count and volume of WMH were imaged at both sites (see complete calibration analysis, figures e-1 to e-3 on the *Neurology*[®] Web site at www.neurology.org). Linear regression demonstrated excellent reproducibility between the 2 MRI scanners ($r = 0.96$ and 0.99 for volume and number of WMH, respectively). Results and analysis are provided for both adjusted and raw FLAIR data.

Analysis of FLAIR images. WMH number and volume quantification was performed as previously described.^{7,13} Briefly, FLAIR images were preprocessed by removal of nonbrain tissue using FSL BET (brain extraction tool), freely available from the Oxford Centre for Functional MRI of the Brain (FMRIB).¹⁴ Next, FLAIR images for individual subjects were registered to their corresponding T1-weighted images using FSL FLIRT (FMRIB's linear image registration tool) and then registered to a common Talairach atlas-based stereotactic frame using FSL FLIRT¹⁵ and 9-parameter (3 each for rotation, translation, and scaling) global normalization transformation. The purpose of this step is to reduce interindividual anatomical variance in the global brain size, shape, and orientation and to permit the use of automated labeling approaches by using a digital brain atlas.¹⁶ Next, all images were corrected for RF inhomogeneity artifact using the FSL BET method with default parameters. RF inhomogeneity artifact manifests itself as a low-frequency variation of MRI intensity that impedes intensity-based image analysis unless corrected. WMH regions were then manually delineated in 3D space using in-house software (<http://ric.uthscsa.edu/mango>) by a single experienced neuroanatomist, blinded for scanner and group information, with high intrarater ($r = 0.95$) test-retest reproducibility and high interrater correlation ($r = 0.92$). During the labeling, WMH regions were coded as ependymal regions, contiguous with CSF structures, and as subcortical regions as previously described.¹⁷ Finally, the volume and location of WMH were analyzed using the boundaries for the frontal, insula, limbic, occipital, parietal, sublobar, and temporal regions extracted from the digital Talairach atlas (<http://www.talairach.org>).

Statistical analysis. Two sets of analyses were performed to compare the prevalence and regional distribution of WMH in pilots to the control group. Group-wise analyses of the difference in the volume and number of WMH were performed using a nonparametric Wilcoxon rank sum 2-tailed statistical model. A nonparametric

test was used because WMH data are not normally distributed. We considered $p < 0.05$ as the threshold for significance. The volume and number of WMH for U-2 pilots were adjusted using the linear regression coefficients obtained from the calibration study to accommodate for a higher signal-to-noise ratio of the Wilford Hall Ambulatory Surgical Clinic imaging center (see figures e-1 to e-3). Group-wise comparison was performed for both original and adjusted data.

Analyses of regional distribution of WMH were performed using the methods described elsewhere.⁷ In short, we performed intergroup comparisons of the volume and number of WMH for the major cerebral partitions based on the 3D Talairach atlas.¹⁸ Further, we tested the regional nonuniformity of lesion distribution by adjusting the fractional volume of lesions per brain region by the fractional volume of region obtained from the atlas. A uniform distribution of lesions would lead to this ratio not being significantly different from the unity. We tested this hypothesis by calculating the significance of the z value obtained by subtracting 1.0 from the normalized fraction of lesion volume and dividing the residual by normalized SD. All regional analyses were performed on raw volume and numbers.

RESULTS An example of punctate subcortical WMH findings in a 39-year-old U-2 pilot who denied ever experiencing symptoms of DCS is shown in figure 1. Population-wide overlap of individual subcortical WMH demonstrated both a much larger number of lesions in pilots and a more uniform regional distribution of WMH than in normal controls (figure 2). Pilots demonstrated a nearly 4-fold increase in volume (375%) and a 3-fold increase in the number (294%) of WMH; this difference was significant for both the raw data and the site-specific adjusted data (table 1). Spearman correlation coefficient between lesion volume and age approached significance for the normal controls but not for the pilots ($p = 0.07$ and 0.16 ; $r = 0.19$ and 0.14 for controls and pilots, respectively) (see figure e-4, top). The correlation coefficients between the number of lesions and age were not different ($p = 0.14$ and 0.2 ; $r = 0.15$ and 0.13 for controls and pilots, respectively) (see figure e-4, bottom). Likewise, the correlation coefficients between the volume and number of WMH and the number of U-2 flight hours were not different

for the pilots ($p > 0.5$; $r = 0.05$ and 0.03 for volume and number, respectively) (see figure e-5).

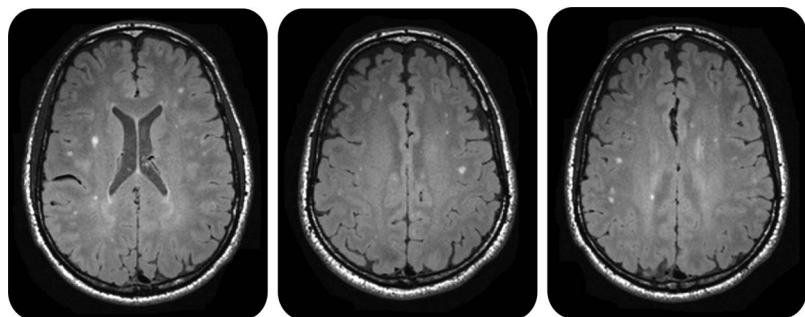
Regional analysis revealed that frontal lobe lesions constituted the largest fraction of both volume and number of WMH loci in both U-2 pilots (50% and 56% for volume and number, respectively) and normative controls (69% and 70% for volume and number, respectively) (see tables e-1 and e-2). Pilots had a higher volume ($p < 0.03$) of WMH in the frontal, insula, limbic, sublobar, and temporal regions and a higher number ($p < 0.01$) of WMH in the insula, limbic, temporal, and sublobar regions. No difference was noted in the occipital and parietal regions. Analysis of regional heterogeneity demonstrated that the fractional WMH volume deviated from the homogeneous distribution for 2 regions in pilots (insula and temporal lobe) vs 5 regions in normal controls (figure 3A). The same analysis was performed on the number of lesions, demonstrating that the regional distribution for pilots relative to the regional volume was more uniform than in the controls (figure 3B).

DISCUSSION The volume and count of WMH are important markers of cerebral integrity.⁹ In addition, increasing volume and number of WMH are linked to age-related cognitive decline, particularly in executive functioning,¹⁹ processing speed, and general cognitive status.²⁰ Histopathologic findings of MRI-localized punctate WMH reveal areas of demyelination and atrophy of the neuropil around fibrohyalinotic arterioles, halo-like rarefaction of myelinated fibers surrounding the atrophic neuropil, and a suggestion of focally decreased permeability of the vessel walls.²¹ There is a significant regional heterogeneity in the distribution of subcortical WMH in normal aging.¹⁰ The majority (60%–80%) of WMH are found in the frontal area, presumably because its high metabolic demand makes it more vulnerable to age-related cerebrovascular disorders,^{22,23} while a more uniform distribution of WMH is a hallmark finding in many neuroinflammatory disorders and traumatic brain injury and may be used to gauge disease severity and progression.^{24,25}

This study demonstrated that pilots exposed to hypobaric had increased volume and number of subcortical WMH compared with a healthy, age- and education-matched normative population. WMH in pilots were more uniformly distributed throughout the brain than in normal controls and did not increase with age in pilots, suggesting that hypobaric exposure produces white matter damage different from that occurring in normal aging. Both findings suggest injury produced by microemboli entering cerebral circulation at random.

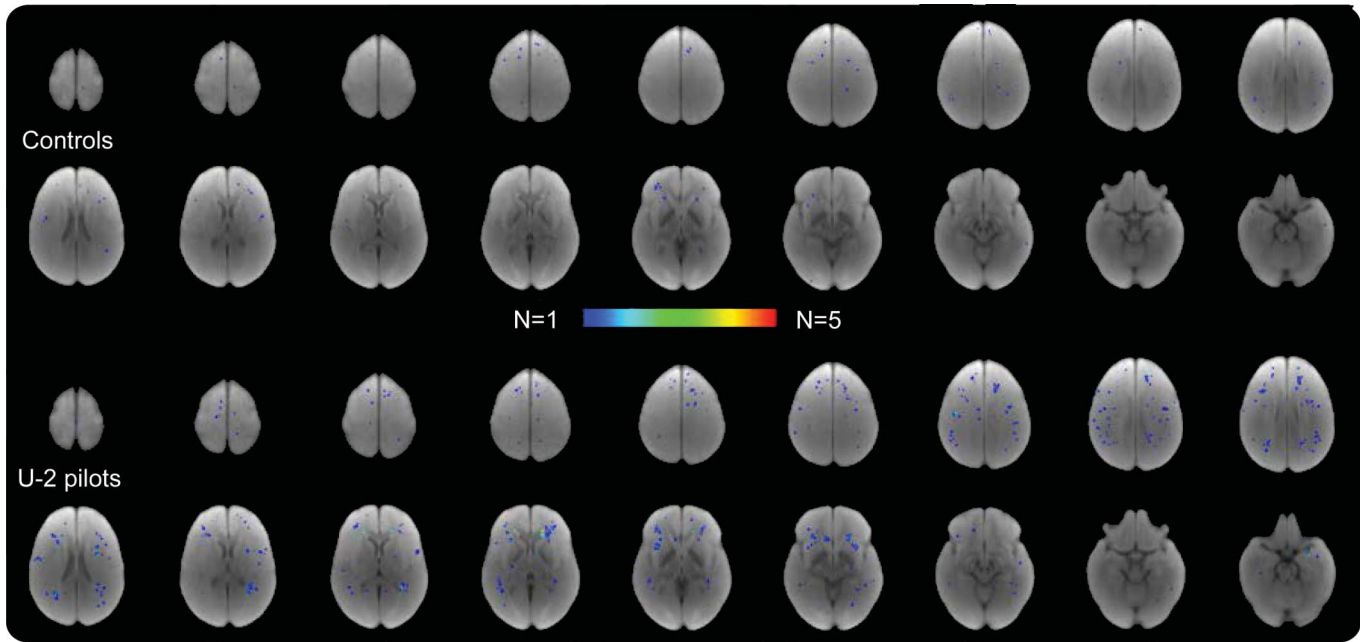
Three potential sources of microemboli should be considered: microbubbles of gas, presumably nitrogen; platelet-based thrombi; and microparticles. The

Figure 1 T2-weighted FLAIR image of a 39-year-old pilot who never experienced NDCS shows multiple punctate WMH



FLAIR = fluid-attenuated inversion recovery; NDCS = neurologic decompression sickness; WMH = white matter hyperintensities.

Figure 2 Summary of WMH lesions for each group



U-2 pilots showed a higher number and a more regionally uniform distribution of lesions, including some overlapping lesions in the frontal area compared with more frontal distribution in controls. WMH = white matter hyperintensity.

symptoms of DCS classically are believed secondary to nitrogen gas bubbles exerting direct pressure on tissues, blocking small arteriolar vessels, and interacting with blood proteins.⁵ All of the WMH observed in pilots were located in deep white matter rather than in the cerebral cortex, suggesting that simple compression of white matter or arteriolar occlusion by gas bubbles cannot be the complete explanation. Additionally, arterial gas emboli are relatively uncommon, reported in only 6 of more than 1,500 altitude chamber exposure cases.²⁶ However, the WMH may still be caused by occlusion or injury to small (5- to 30- μ m) deep cerebral vessels from microembolic gas bubbles that are smaller than the 30- μ m detection limit of clinical ultrasound scanners used for bubble detection.²⁷ A second potential mechanism is occlusion of small cerebral vessels by platelet thrombi produced by accelerated coagulation of blood in the presence of venous nitrogen gas bubbles; in rabbits, microthrombi were noted in medium-sized and large lung arteries after DCS.²⁸

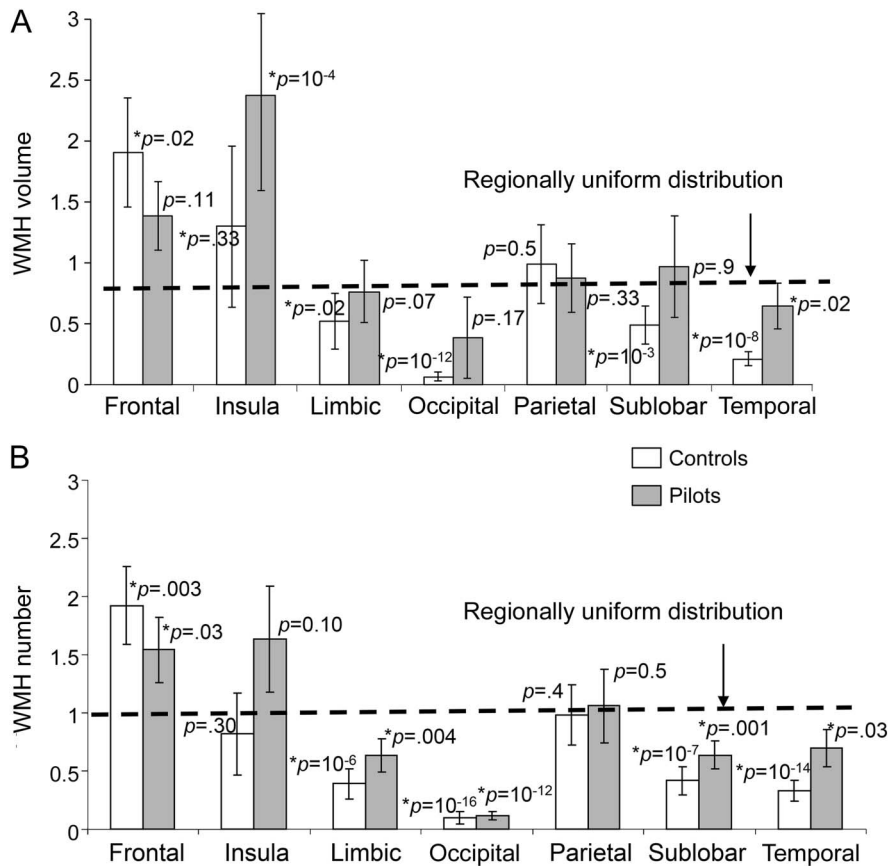
This mechanism is also supported by the decreased platelet count with increased concentration of venous nitrogen gas bubbles in humans due to increases in platelet adhesion and aggregation.²⁹ A third potential mechanism is microparticle release, 0.1- to 1.0- μ m vesicles with proinflammatory potential, with induction of neutrophil activation and vascular damage in response to intravascular bubbles as demonstrated in mice.³⁰ In scuba divers, microparticles are increased 3.4-fold, neutrophil activation occurs, and increased neutrophil interactions with platelet membranes are noted.³¹ Such an inflammatory mechanism might explain the clinical relapse we observed in 3 NDCS pilots after successful hyperbaric treatment (US Navy Treatment Table 6; 100% fraction of inspired oxygen; 2.8 atm absolute) when subsequently exposed to commercial airline cabin altitudes within the first 2 weeks after the incident. Further studies in laboratory animals are necessary to clarify the precise pathologic mechanisms responsible for formation of hypobaric-induced WMH.

Table 1 Whole-brain volume and number of WMH for pilots vs controls

	Doctorate-degree normal controls (n = 82)	U-2 pilots (original) (n = 105)	U-2 pilots (adjusted) (n = 105)	Wilcoxon rank sum 2-tailed p value	
				Original	Adjusted
WMH volume, mean \pm SD, cm ³	0.042 \pm 0.071	0.134 \pm 0.271	0.155 \pm 0.313	0.009	0.004
WMH count, mean \pm SD	3.29 \pm 4.49	7.57 \pm 14.31	9.67 \pm 18.26	0.020	<0.001

Abbreviation: WMH = white matter hyperintensity.

Figure 3 Regional uniformity of WMH lesion distribution was tested by calculating the fraction of WMH volume (A) and numbers (B) over the fractional volume of each brain region



Regional uniform distribution for WMH lesions, where the lesion volume and number are explained by volume of the region, corresponds to ratios that are not significantly different from the unity (1.0). Pilots demonstrate a more uniform distribution than controls. WMH = white matter hyperintensity.

Increased WMH burden was previously reported in high-altitude mountain climbers, attributed to a combination of hypoxia and hypobaria.^{32,33} Oxygenation status was maintained in our pilots; therefore, we can exclude hypoxia as a potential cause of our increased WMH.³⁴ Another argument for ruling out hypoxia is increased WMH in divers who experience decompression going from depths to sea level. Increased WMH were detected in 23% (26/113) of Turkish military divers without a history of DCS compared with 11% (7/65) of controls.³⁵ Similarly, an increase in WMH was observed in French military divers lacking a history of DCS when compared with normal controls.³⁶ This suggests that the prevalence of WMH is increased in populations whose occupation subjects them to deviations in atmospheric pressure.

Our study suggests that occupational exposure to hypobaria induces WMH, presumably secondary to white matter injury, even in the absence of clinical symptoms of NDCS. The etiology of this is unknown but is believed to be secondary to microembolic gas bubbles, “thrombo-inflammatory” mechanisms, or microparticle-induced neutrophil activation and vascular

damage rather than simple gas bubble occlusion of cerebral arterioles. Our study provides radiologic evidence supporting the premise of microemboli showering cerebral tissues and provides evidence of cerebral injury as a consequence of this activation. Cerebrovascular-induced WMH is typically permanent, but the long-term ramifications of hypobaric-induced WMH are unknown. More complete understanding of this pathologic mechanism will require development of a laboratory animal model of hypobaria-related white matter damage to detect the biological/neuropathologic mechanism and to develop neuroprotection/neurotreatment therapies designed to mitigate this damage.

AUTHOR CONTRIBUTIONS

Dr. McGuire: study concept, design, performance analysis, interpretation, and principal author of the manuscript. Dr. Sherman: study concept, design, performance, analysis and interpretation. Dr. Profenna, Dr. Grogan, Dr. Sladky, Dr. Brown, and Dr. Robinson: acquisition of data, analysis and interpretation. Dr. Rowland, Dr. Hong, and Ms. Patel: analysis and interpretation. Dr. Tate: analysis, interpretation, and critical revision of the manuscript for important intellectual content. Ms. Kawano: critical scientific editorial assistance. Dr. Fox: study concept and design. Dr. Kochunov: study concept, design, performance, data analyses, and critical revision of the manuscript for important intellectual content.

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DISCLOSURE

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