White Matter Integrity in High-Altitude Pilots Exposed to Hypobaria

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INTRODUCTION: Nonhypoxic hypobaric (low atmospheric pressure) occupational exposure, such as experienced by U.S. Air Force U-2 pilots and safety personnel operating inside altitude chambers, is associated with increased subcortical white matter hyperintensity (WMH) burden. The pathophysiological mechanisms underlying this discrete WMH change remain unknown. The objectives of this study were to demonstrate that occupational exposure to nonhypoxic hypobaria is associated with altered white matter integrity as quantified by fractional anisotropy (FA) measured using diffusion tensor imaging and relate these findings to WMH burden and neurocognitive ability.

METHODS: There were 102 U-2 pilots and 114 age- and gender-controlled, health-matched controls who underwent magnetic resonance imaging. All pilots performed neurocognitive assessment. Whole-brain and tract-wise average FA values were compared between pilots and controls, followed by comparison within pilots separated into high and low WMH burden groups. Neurocognitive measurements were used to help interpret group difference in FA values.

RESULTS: Pilots had significantly lower average FA values than controls (0.489/0.500, respectively). Regionally, pilots had higher FA values in the fronto-occipital tract where FA values positively correlated with visual-spatial performance scores (0.603/0.586, respectively). There was a trend for high burden pilots to have lower FA values than low burden pilots.

DISCUSSION: Nonhypoxic hypobaric exposure is associated with significantly lower average FA in young, healthy U-2 pilots. This suggests that recurrent hypobaric exposure causes diffuse axonal injury in addition to focal white matter changes.

KEYWORDS: White matter integrity, hypobaric exposure, U-2 pilots.

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Nonhypoxic hypobaric (low atmospheric pressure) occupational exposure, such as experienced by U.S. Air Force (USAF) U-2 pilots and inside safety personnel operating altitude chambers, is associated with increased subcortical white matter hyperintensity (WMH) burden.[17,18] The pathophysiological mechanisms underlying this discrete WMH change remain unknown. WMH are regions of accumulation of extracellular water due to focal degradation of the myelin sheath,[5] and the volume of WMH is a nonspecific marker of cerebral integrity sensitive to multiple etiologies.[14] We posited that hypobaric exposure would be associated with diffuse microstructural alteration in normal-appearing cerebral white matter (WM) as measured by diffusion tensor imaging (DTI) and that higher WMH burden would be associated with more diffuse alterations. We also posited that decreased microstructural integrity in normal-appearing WM would be associated with a decrement in neurocognitive function, similar to the lower neurocognitive performance previously associated with WMH burden.[19]

DTI is a quantitative magnetic resonance imaging (MRI) technique that has an advantage over T2-weighted fluid attenuated inversion recovery (FLAIR) imaging because it can ascertain subtle WM damage in normal-appearing WM prior to development of WMH lesions.[15] Fractional anisotropy (FA) is a widely used quantitative measure of WM microstructure,

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extracted from DTI.[2] FA is an important biomarker in clinical studies as it can sensitively track WM changes in neurological and psychiatric diseases[10,22,25] and in normal development and aging.[14] Toward this aim we compared FA data for USAF U-2 pilots to similar, healthy, high-functioning controls (CTRL) lacking repetitive hypobaric exposure. USAF pilots are uniquely high-performing individuals, especially in the visual-spatial and processing speed domains.[3] We used the scores from the USAF-administered neurocognitive test of visual-spatial performance to interpret the findings of regional differences in DTI-FA.

METHODS

Subjects

The study was reviewed and approved by the Air Force Research Laboratory Institutional Review Board. All pilot and control subjects were active duty members of the U.S. Armed Forces. Calibration (CAL) subjects, recruited to permit cross-comparison of the two scanners utilized in this study, were active duty or retired military beneficiaries. All participants were recruited with strict adherence to the Department of Defense Instruction for Protection of Human Subjects.[4] For all subjects, participation was voluntary without commander involvement or knowledge. All subjects provided informed consent prior to participation. Subjects did not receive compensation for participation, but subjects' travel costs were reimbursed as permitted under Federal Government travel regulations.

All active duty pilots were invited to participate, with $N = 106$ accepting for a participation rate exceeding 90%; 3 subjects lacking FA data and 1 with corrupted data from acquisition error at time of MRI were subsequently excluded. All pilots had a history of recurrent occupational exposure to nonhypoxic hypobaric cabin altitudes (8534-9144 m; 28,000-30,000 ft) that lasted up to 9 h and that occurred with a variable frequency but not more often than every 3rd day. There were 22 (21%) pilots who reported a history of mission-related symptoms of neurological decompression sickness, but all were healthy at the time of imaging and on unrestricted active flying status. All pilots undergo standardized hypoxic hypobaric chamber exposure as part of routine aircrew qualification training every 5 yr; these exposures are of 30-60 min duration with hypoxia relieved with 100% oxygen delivered via an aviator mask upon the onset of physiological symptoms. Pilots were predominantly male (M/F 100/2), reflecting the current USAF U-2 pilot sex distribution. Male and female ages were similar [all/male/female mean age 37.9 $\pm$ 6.0 yr (range 28-50)/37.9 $\pm$ 6.0 (28-50)/38.0 $\pm$ 2.0 (36-40); $P > 0.1$].

Controls ($N = 114$) assigned to duty within the continental United States were recruited through presentations at professional staff and international aerospace meetings and through electronic messaging. All controls possessed a doctorate degree to permit cross-comparison to pilots (published mean intelligence quotient of controls 125; measured mean intelligence quotient of pilots 126). Controls were predominantly from the two San Antonio graduate medical education military facilities. Controls were age and gender controlled [gender M/F 109/5; ages all/male/female mean age 34.9 $\pm$ 6.0 yr (range 26-50)/34.8 $\pm$ 6.0 (26-50)/38.4 $\pm$ 2.0 (36-44); $P > 0.1$].

All pilots met USAF Flying Class II standards and were on active USAF flying status. All control subjects met neurological standards for USAF Flying Class II but were not on flying status. 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 for control; hyperlipidemia requiring more than a single statin for control; diabetes or glucose intolerance; any neurological disease including infection, seizure, or stroke; familial history of degenerative neurological disease; substance or drug abuse; or any systemic disease with the potential for neurological involvement.

Calibration subjects ($N = 46$; average age 40.0 $\pm$ 10.8 yr, range 22-61 yr; M/F 29/17) were military beneficiaries recruited from the San Antonio area. Subjects were permitted to have mild medical illnesses such as controlled hypertension on a single ACE-inhibitor and hyperlipidemia on a single low dose statin so that a spectrum of WMH burden would be represented; exclusionary criteria included diabetes, history of central nervous infection, substance or drug abuse, degenerative/inflammatory/autoimmune neurological disease, stroke, or significant head trauma. We accepted the first 46 who were available for imaging at both MRI scanners on the same day and met entry criteria.

Procedure

Pilot imaging data were collected at the Research Imaging Institute (RII), University of Texas Health Science Center, San Antonio, TX, using a Siemens 3T Tim Trio scanner equipped with a 12-channel phase array coil. Control imaging data were collected at the Wilford Hall Ambulatory Surgical Center (WH), 59th Medical Wing, Joint Base San Antonio – Lackland, TX, using a Siemens 3T Verio scanner equipped with a 32-channel phase array coil. Calibration imaging data were obtained at both RII and WH. Both scanners are operated under quality control and assurance guidelines in accordance with recommendations by the American College of Radiology. Three-dimensional fluid attenuated inversion recovery (FLAIR) was utilized for WMH analysis as previously described.[18] Briefly, FLAIR images were coregistered to a common Talairach-atlas-based stereotactic frame. An experienced neuroanatomist blinded to group as previously described manually traced WMH[17] while a neuroradiologist blinded to clinical history provided MRI interpretation. For each lobe we manually counted the number of WMH (count) and used in-house software (PVK) to compute the total volume of WMH (volume). WMH were divided into periventricular (adjacent to the ventricles) and subcortical; we considered only the subcortical WMH burden to be significant since only the subcortical WMH burden correlates with hypobaric stress.[17] Three-dimensional imaging parameters were T1 MPRAGE: repetition time (TR) = 2200 ms, echo time (TE) = 2.85 ms, isotropic resolution 0.80 mm, and FLAIR: TR = 4500 ms, TE = 1 ms, and isotropic resolution 1.00 mm.

High angular resolution diffusion imaging (HARDI) was utilized for DTI and FA as previously reported.[9] Briefly, DTI data were collected using a single-shot echo-planar, single refocusing spin-echo, T2-weighted sequence with a spatial resolution of 1.7 × 1.7 × 3.0 mm with sequence parameters of TE/TR = 87/8000 ms, field of view = 200 mm, axial slice orientation with 50 slices and no gaps, 64 isotropically distributed diffusion weighted directions, two diffusion weighting values ($b = 0$ and 700 $s \cdot mm^{-2}$), and five $b = 0$ images. HARDI data for both groups were processed using the freely available ENIGMA (Enhanced Neuroimaging Genetics through Meta-Analysis)-DTI pipeline (http://enigma.ini.usc.edu/protocols/dti-protocols/)[8] which consists of a set of protocols and scripts to measure average whole-brain FA value and average tract FA values for 10 major WM tracts (corpus callosum, corticospinal, internal capsule, corona radiata, thalamic radiation, sagittal stratum, external capsule, cingulum, superior longitudinal fasciculus, and fronto-occipital). We chose the ENIGMA-DTI analysis protocol because it can effectively overcome the impact of the punctate WMH lesions on FA values compared to simple averaging of FA values within a region of interest, effectively limiting analysis of FA values to that of the normal-appearing WM.

All pilots performed MicroCog neurocognitive assessment as previously described.[19] Briefly, this computer-based assessment evaluates key neurocognitive functioning in USAF personnel in five content-specific domains (attention/mental control, reasoning/calculation, memory, spatial processing, reaction).[3,20] Previously, we showed that high WMH load in U-2 pilots was associated with uniformly lower performance in reasoning/calculation and memory domains when compared to USAF pilot controls. In this manuscript, the spatial cognitive performance scores were used to explain the population differences in regional FA values between pilots and controls with similar cognitive abilities.

Statistical Analysis

FA values for the pilot group were scaled using linear regression calibration coefficients (slope and bias) derived from $N = 46$ calibration (CAL) DTI data collected on two scanners. For calculation of the scaling factors between scanners we employed regression analysis, coefficients of variation, and difference of the mean values. We set our outer limits for inclusion as ± 3 SD. To minimize environmental and biological factors that may influence FA values, CAL were imaged the same day on both scanners with random assignment to first scanner used.

We utilized the freely available R Project for Statistical Computing[23] functions of generalized linear model (GLM), Kolmogorov-Smirnov (KS), Wilcoxon rank test, TTEST, and Pearson's correlation for statistical relevance. For GLM calculations we used subjects' age as a nuisance covariate. We selected the KS test as our primary test, as it is a more conservative statistical test for comparison of FA values; GLM was more liberal and tended to demonstrate overall more significant *P*-values. We used the Wilcoxon rank sum test for comparison of nonparametric WMH burden and we used the TTEST for comparison of neurocognitive testing results. We also used Pearson's correlation test for comparison of neurocognitive to FA results.

We considered $P \leq 0.05$ as significant. We applied the Bonferroni multiple test correction for determination of by-tract significance and considered the Bonferroni adjusted $P \leq 0.05$ as significant.

RESULTS

The calibration for the average FA values in subjects imaged on both scanners showed excellent correlation (r = 0.85). Coefficients of variation were 3.83% (RII) and 4.03% (WH), similar to other reports.[7,21] Significant correlations (r = 0.65-0.83; $P < 0.045$ after correcting for $N = 9$ comparisons) were observed for all regional FA tracts with the exception of the corticospinal tract (r = 0.45). WH mean values were 1.5–8.9% greater than raw RII values except for the corticospinal tract (17.9% difference). We excluded the corticospinal tract from further analysis as the test-retest reliability shows that we cannot reliably measure FA for this tract. Similar observations were reported by other studies (**Table I**).[12,13]

Whole-brain average FA values for all pilots were significantly lower than in controls (KS $P < 0.001$; GLM $P < 0.001$; **Fig. 1**). After Bonferroni correction of *P*-values, we observed

Table I. CAL Mean ± SD. Values for RII and WH with Regression-Derived Scaling Factors.

					RII		WH			
CAL	SLOPE	INTERCEPT	r^2	r	MEAN ± SD	COEFF VAR (%)	MEAN ± SD	COEFF VAR (%)	COUNT	RII-WH DIFFERENCE (%)
AvgFA	0.955	0.054	0.721	0.849	0.468 ± 0.018	3.83	0.501 ± 0.020	4.03	45	6.5
CC	0.627	0.298	0.497	0.705	0.744 ± 0.034	4.58	0.764 ± 0.030	3.97	46	2.6
CS	0.454	0.446	0.201	0.448	0.584 ± 0.040	6.93	0.711 ± 0.041	5.76	45	17.9
IC	0.648	0.276	0.391	0.625	0.640 ± 0.023	3.59	0.690 ± 0.024	3.45	46	7.3
CR	0.878	0.071	0.687	0.829	0.518 ± 0.024	4.63	0.526 ± 0.025	4.83	46	1.5
TR	0.790	0.176	0.685	0.828	0.606 ± 0.0	5.12	0.654 ± 0.030	4.52	46	7.4
SS	0.778	0.168	0.659	0.812	0.568 ± 0.035	6.20	0.610 ± 0.034	5.53	46	6.9
EC	0.8	0.126	0.604	0.777	0.503 ± 0.027	5.32	0.544 ± 0.029	5.26	46	7.5
Cing	0.786	0.168	0.622	0.788	0.657 ± 0.038	5.79	0.685 ± 0.038	5.54	46	4.0
SLF	0.758	0.156	0.573	0.757	0.518 ± 0.024	4.73	0.548 ± 0.024	4.47	46	5.6
FO	0.690	0.223	0.421	0.649	0.548 ± 0.035	6.33	0.601 ± 0.037	6.14	46	8.9

Note: CAL = calibration; RII = Research Imaging Institute; WH = Wilford Hall. Count = number of subjects studied. Average global brain (Avg FA), corpus callosum (CC), corticospinal (CS), internal capsule (IC), corona radiata (CR), thalamic radiation (TR), sagittal stratum (SS), external capsule (EC), cingulum (Cing), superior longitudinal fasciculus (SLF), and fronto-occipital (FO).

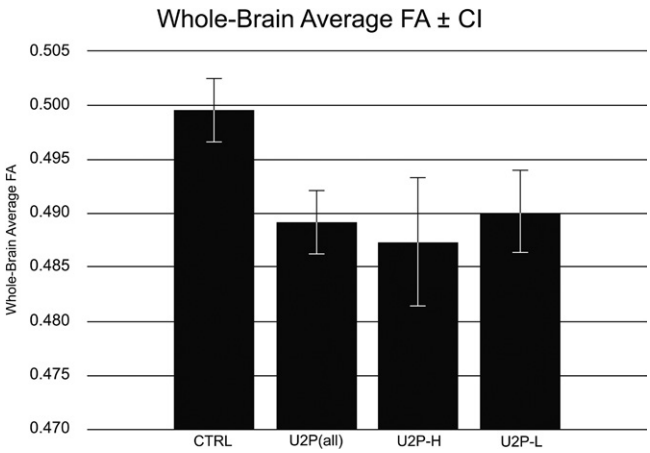

Fig. 1. Whole-brain average fractional anisotropy expressed as Mean ± CI. CTRL = control; U2P = entire U-2 pilot population; U2P-H = high white matter hyperintensity (WMH) burden subset; U2P-L = low WMH burden subset.

two regional findings: pilots had significantly decreased FA values for sagittal stratum ($P < 0.001$), while pilots had significantly higher FA values for fronto-occipital fibers ($P = 0.003$). Other FA tracts were not significantly different.

Next, we separated the pilots into lower two-thirds (U2P-L)/upper one-third (U2P-U) based on WMH burden (U2P-L/U2P-H). There was no significant difference in WMH burden between U2P-L and controls (CTRL) (WMH volume/count $P = 0.17/0.52$, respectively), while there was a significant difference between U2P-H/U2P-L ($P < 0.001/<0.001$) and U2P-H/CTRL ($P < 0.001/<0.001$). Comparing FA values of U2P-H and U2P-L to CTRL demonstrated significantly lower FA values in both pilot groups for whole brain average FA ($P < 0.001/P < 0.001$, respectively, U2P-H/U2P-L) and sagittal stratum ($P = 0.005/P = 0.01$). Comparing mean values of U2P-H to U2P-L demonstrated a nonsignificant trend toward lower FA values in U2P-H than U2P-L for whole-brain average FA and all tracts except fronto-occipital where U2P-H = U2P-L (**Table II**).

Of the five primary cognitive domains assessed by the MicroCog, significant positive correlation was noted between whole-brain average FA and spatial processing (Pearson's coefficient = 0.2632; $P = 0.009$). The positive correlation with spatial processing after Bonferroni correction was significant only for the corpus callosum tract.

DISCUSSION

We previously demonstrated a significant increase in subcortical punctate white matter (WM) abnormalities in U-2 pilots occupationally exposed to nonhypoxic hypobaria.[17,18] The present study extends this work by assessing the integrity of the normally appearing cerebral WM in the same cohort. We observed a significantly lower ($P < 0.001$) average FA value in the pilot cohort compared to normal controls that is consistent with a diffuse disruption in white matter integrity, driven by subjects with high WMH burden. While the pilots with low WMH burden demonstrated a trend toward higher average FA values when compared to pilots with high WMH burden this difference was not statistically different ($P > 0.05$) and warrants further investigation.

Two findings were noted during tract analysis. The sagittal stratum FA values were significantly reduced in pilots compared to controls. In contrast, pilots had significantly higher FA values in the fronto-occipital fibers. Notably reduced sagittal stratum FA was shown to be genetically associated with processing speed deficits in two independent cohorts.[11] We previously observed a decrease in processing speed in U-2 pilots compared to a USAF pilot control cohort[19] and, thus, this may suggest the reduced sagittal stratum FA in U-2 pilots may explain this decrease in processing speed. Additionally, USAF pilots are uniquely high-functioning individuals with exceptional visual-spatial abilities,[3] which may account for the higher FA values in the fronto-occipital fibers in U-2 pilots, reflecting this associative cognitive ability, and provide an anatomical basis for the superior spatial performance noted in all USAF pilots.

Historically, the pathophysiological theory of the hypobaric related brain damage is focused on preventing the arterial gas emboli that are thought to be the underlying etiology, although more recent work suggests a more diffuse process.[1,6] We believe

Table II. Whole-Brain Average and Tract FA Values.

FA TRACT	CTRL (*N* = 114)	U2P-H (*N* = 34)	U2P-L (*N* = 68)	CTRL:U2P KS/ BONFER *P*-VALUE	CTRL:U2P-H KS *P*-VALUE	CTRL:U2P-L KS *P*-VALUE	U2P-H:U2P-L KS *P*-VALUE
Avg FA	0.500 ± 0.016	0.487 ± 0.018	0.490 ± 0.018	<0.001	0.001	0.001	0.593
CC	0.757 ± 0.025	0.754 ± 0.018	0.757 ± 0.022	0.842/1.0	0.793	0.863	0.711
IC	0.688 ± 0.024	0.693 ± 0.021	0.695 ± 0.019	0.093/0.841	0.052	0.138	0.480
CR	0.525 ± 0.021	0.532 ± 0.020	0.536 ± 0.023	0.047/0.421	0.150	0.056	0.379
TR	0.656 ± 0.028	0.640 ± 0.030	0.646 ± 0.026	0.033/0.300	0.101	0.078	0.822
SS	0.609 ± 0.030	0.588 ± 0.035	0.594 ± 0.028	<0.001/<0.001	<0.001	<0.001	0.480
EC	0.540 ± 0.024	0.542 ± 0.025	0.546 ± 0.021	0.412/1.0	0.610	0.330	0.822
Cing	0.685 ± 0.034	0.662 ± 0.033	0.671 ± 0.032	0.010/0.092	0.039	0.064	0.822
SLF	0.551 ± 0.026	0.554 ± 0.024	0.554 ± 0.023	0.5/1.0	0.879	0.234	0.822
FO	0.586 ± 0.036	0.603 ± 0.026	0.603 ± 0.024	<0.001/0.003	0.018	<0.001	0.711

CTRL = control; U2P = entire U-2 pilot population; U2P-H = high WMH burden subset; U2P-L = low WMH burden subset. KS = Kolmogorov-Smirnov test; Bonfer = Bonferroni adjusted *P*-value. Average global brain (Avg FA), corpus callosum (CC), internal capsule (IC), corona radiata (CR), thalamic radiation (TR), sagittal stratum (SS), external capsule (EC), cingulum (Cing), superior longitudinal fasciculus (SLF), and fronto-occipital (FO).

that gaseous macrobubbles alone could not produce the diffuse disruption of axonal integrity[24] and this study adds additional support for other potential pathophysiological explanations, including neuroinflammation and microparticle damage[26] and supports pursuing a more comprehensive etiological explanation of hypobaric-induced neurological injury extending beyond simple arteriolar occlusion.

A potential significant limitation of this study is the equivalency of these two cohorts. We addressed this by controlling for age, gender, and comorbid medical conditions. Additionally, restricting this study to active duty military volunteers routinely subjected to military-mandated health and drug monitoring further controls for unrecognized health or abuse problems.

Another potential limitation is the equivalency of the two scanners used. We addressed this by utilizing the same protocol across the two Siemen scanners in a large calibration cohort of 46 subjects to establish a calibration coefficient. We believe that high r-values (except for the excluded corticospinal tract) and low coefficients of variation justify direct correlation of results between these two scanners. Our calibration results are similar to other interscanner correlation reports.[7,16]

Although 98% of our pilot subjects are male, post hoc analysis yielded similar results to the entire population analysis; therefore, these findings may be generalizable to both genders exposed to such environmental conditions.

This study clearly mandates the need for further research. While none of these subjects had any functional deficit, we postulate this may simply be a reflection of their high degree of premorbid functioning and the relatively small deficits detected. However, this does raise the possibility that a more intense or prolonged exposure might lead to a functional deficit. Additionally, the diffuse disruption of axonal integrity suggests a need to better understand the underlying pathophysiology to permit implementation of improved mitigation and/or treatment modalities. Having established that hypobaric exposure is associated with WM injury, the next step is the development of an animal model to better understand the mechanism of recurrent hypobaric exposure injury and the elaboration of strategies to minimize its impact on cerebral health.

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