Increased CBF Related to High Altitude Exposure – MRI Assessment of Aircrew in the Hypobaric Environment

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14 Sep 2017
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.

Radiologist/Neuroradiologist
Prior Senior Flight Surgeon

U.S. Air Force photo by A1C Zade C. Vadnais
Neurologic Decompression Sickness (NDCS) Background

- Increased incidence of NDCS associated with recent conflict
  - 1955-1998 no “reported” type II
    - 1996 anonymous survey 75.5% during career noted DCS
  - 2002-2009 16 confirmed NDCS events (5 near-fatal)
  - 1994-2005
    - DCS risk 0.076%/flight
    - 0-5 cases/yr
    - 10 type II/12 yr
  - 2006-2010
    - 300% increased rate of NDCS
    - DCS risk 0.23%/flight
    - 6-10 cases/yr
    - 22 type II/5 yr
- Research prompted by 5 near fatalities (2009-2010)
  - U2P imaging began 5/2011

Jersey et al. Aviat Space Environ Med 2010;81:64-8
Jersey et al. Aviat Space Environ Med 2011;82:673-828
Hundemer et al. Aviat Space Environ Med 2012;83:968-74
MRI in U2P (U-2 Pilots) With & Without Clinical NDCS

Phase 1
#s:
U2: 106
AOP/PHY: 83
Controls/Docs: 162
MRI in AOP (Chamber) With & Without Clinical NDCS
Significantly increased subcortical white matter hyperintensity (WMH) volume/count in U2P & AOP/PHY

AFC ≈ DOC ≈ NOR

U2P ≈ AOP/PHY ≈ FSG

* Individual variability*

Volume probably more clinically significant

<table>
<thead>
<tr>
<th></th>
<th>DOC</th>
<th>U2P</th>
<th>PHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH vol (mean±CI)</td>
<td>0.035±0.009</td>
<td>0.129±0.049</td>
<td>0.126±0.086</td>
</tr>
<tr>
<td>WMH cnt</td>
<td>2.8±0.5</td>
<td>7.5±2.7</td>
<td>6.4±2.4</td>
</tr>
</tbody>
</table>

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

Subcortical WMH volume known to increase with advanced age (> ~ 60yr)
• 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
Little correlation between total hours of exposure and subcortical WMH burden*

Suggests multi-factor relationship to WMH burden
Phase 1 Repetitive Exposure
Fractional Anisotropy

- 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 MRI scanners
  - 46 subjs dual imaged (r=0.85; COV=4%)

McGuire et al. Aerosp Med Hum Perform 2016; 87:983-988
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 injury
- Multiple measures indicate pilots similar at UPT
- Decrease suggests diffuse white matter process

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

McGuire et al. Neurology 2014;83:638-645
### Phase 1 Repetitive Exposure Neurocognitive Differences

**MicroCog absolute values generally decreased with greater WMH burden within the U2P population (nonsignificant trends)**

<table>
<thead>
<tr>
<th>Level</th>
<th>MicroCog (current)</th>
<th>Lower WMH Burden</th>
<th>Upper WMH Burden</th>
<th>t-test (2-tailed) Significance</th>
<th>Sidak (2-tailed) Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Count (n=36)</td>
<td>Volume (n=33)</td>
<td>Count (n=65)</td>
<td>Volume (n=68)</td>
</tr>
<tr>
<td>1</td>
<td>Attention/mental control</td>
<td>105.8</td>
<td>105.9</td>
<td>105.0</td>
<td>105.0</td>
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<tr>
<td>1</td>
<td>Reasoning/calculation</td>
<td>104.8</td>
<td>102.8</td>
<td>97.5</td>
<td>98.8</td>
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<tr>
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<td>Memory</td>
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<td>110.4</td>
<td>110.3</td>
<td>108.3</td>
<td>108.4</td>
</tr>
<tr>
<td>1</td>
<td>Reaction time</td>
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<td>109.6</td>
<td>107.0</td>
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<td>2</td>
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<td>105.0</td>
<td>102.7</td>
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<td>2</td>
<td>Information processing accuracy</td>
<td>105.2</td>
<td>105.3</td>
<td>100.8</td>
<td>100.9</td>
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<tr>
<td>3</td>
<td>General cognitive functioning</td>
<td>107.4</td>
<td>106.4</td>
<td>102.2</td>
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Phase 1 Repetitive Exposure Summary

- Acquired increase in discrete subcortical WMH lesions
  - Presumably reflects permanent glial scarring in WM

- Acquired decrease in FA in normal appearing WM (U2P & ? PHY)
  - Reflects axonal integrity loss – segregates with WMH burden

- Acquired decrease in neurocognitive functioning
  - Decrease corresponds to degree of WMH burden
  - Includes speed of processing and executive functioning
  - Corresponds to diffuse axonal injury pattern

- Complex pathophysiological process
  - **Intensity of exposure** (frequency, duration, physical activity, etc.)
  - Individual biovariability and susceptibility

- Relative contribution from hypobaria and/or pre-breathe hyperoxia unknown
Single Exposure Study

Hypothesis – single occupational exposure to hypobaria and/or hypoxia will be associated with transient MRI and serological changes

• Earliest MRI changes will be in MRS, DTI/Q-space, and arterial blood flow
• Transient microparticle increase will parallel changes noted in divers
• Inflammatory serological markers will be up-regulated

Permanent MRI change is associated with recurrent and frequent nonhypoxic hypobaric exposure
Single Exposure Study

Four limbs – all meet FCII/FCIII neurological standards
  • Hypobaric-hypoxic (AFC traditional aircrew chamber training)
  • Hypobaric (AOP inside safety monitors)
  • Hypoxic (ROBD – reduced $O_2$ breathing device)
  • Control (NOR)

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

Intra-subject and cross-group comparisons
Single Exposure Study

Study began Sep 2014, just closed to recruitment in Aug 2017

Original goal: 50 subjects in each of the 4 limbs
  • Focus changed to AFC and NORM after realization of recruitment limitations

Total imaged: 186

AFC group: 96
  • 65 males, 31 females

NORM group: 73
  • 66 males, 7 females

AOP: 14
  • 7 males, 7 females

ROBD: 3
  • 3 males

Phase 1 and 2 studies: 536 subjects imaged
Phase 2 Single Exposure
Arterial Blood Flow (ASL)

Increase in WM CBF at 24/72hr (WM ↑ possibly precedes GM ↑)
  • Significant group (AFC vs. NOR) difference
    • WM p<0.001 (Utilized generalized additive model adjusted for age and gender)

Potentially similar change in AOP group (“n” too small for assessment)
Phase 2 Single Exposure
WMH Burden

- No significant difference for subcortical WMH FLAIR group difference
- A single exposure does not increase WMH burden
  - Repetitive exposure in U-2 pilots demonstrates apparent acquired increased subcortical WMH burden
Phase 2

- Metabolic changes demonstrated with MRS
  - Will be discussed by Dr. McGuire
- Challenges with serology

- No additional airframe /pilots imaged to date
  - USN study to image F/A-18 pilots will begin later this year
Summary

Recurrent exposure to nonhypoxic extreme hypobaria incites:
- Focal punctate subcortical white matter hyperintensities (WMH) on MRI
- Diffuse decrement in axonal integrity on MRI
- Acquired neurocognitive decline as measured on CBT

Single exposure to extreme hypobaria (routine occupational aircrew training) incites:
- Increase in white matter followed by gray matter cerebral blood flow that persists at 72 hours post-exposure on MRI

Additional MRI findings will be discussed by Dr. McGuire
Aerospace Relevance

- Recurrent unexplained physiological events effecting all 4th and 5th generation fighter aircraft (F-16, F/A-18, F-22, F-35)
- Anecdotal reports from CCAT personnel of unexplained neurological worsening in acute TBI warriors associated with A/E flights
- Unexplained increased white matter hyperintensity (WMH) burden in astronauts
- Long-term neurocognitive functioning impact/disability in exposed individuals
- Poorly defined risk factors

- Potentially impacting any warrior subjected to decompressive stress
  - High altitude drops (SFO, aircrew)
  - High altitude ops in unpressurized platforms (rotary, etc.)
  - SCUBA divers
QUESTIONS?