EXPLORATORY ANALYSIS OF CARBON DIOXIDE LEVELS, ULTRASOUND AND OPTICAL COHERENCE TOMOGRAPHY MEASURES OF THE EYE DURING ISS MISSIONS

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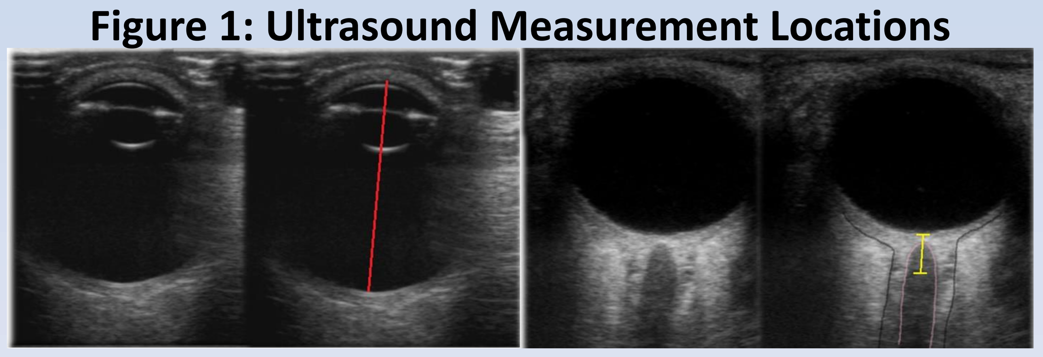
Background

Carbon dioxide (CO_2) levels onboard the International Space Station (ISS) have typically averaged 2.3 to 5.3 mmHg, with large fluctuations occurring over periods of hours and days. CO_2 has effects on cerebral vascular tone, resulting in vasodilation and alteration of cerebral blood flow (CBF). Increased CBF leads to elevated intracranial pressure (ICP), a factor leading to visual disturbances, headaches, and other central nervous system symptoms. Ultrasound of the optic nerve and optical coherence tomography (OCT) provide surrogate measurements of ICP; in-flight measurements of both were implemented as enhanced screening tools for the Visual Impairment/Intracranial Pressure (VIIP) syndrome. This analysis examines the relationships between ambient CO_2 levels on ISS, ultrasound and OCT measures of the eye in an effort to understand how CO_2 may possibly be associated with VIIP and to inform future analysis of in-flight VIIP data.

Methods

Ultrasound measurements of the eye were collected on flight days 30, 90, and R-30 (±7 days), and included optic nerve diameter (OND), optic nerve sheath diameter (ONSD), and anterior-posterior (AP) diameter. OND and ONSD were measured in a standardized axial plane avoiding the anterior chamber of the eye. OND and ONSD are assessed at 3mm from the retinal interface (yellow line in Fig. 1). AP diameter was measured in the near-axial plane adjusted to pass through the corneal vertex and the optic nerve head (red line in Fig. 1). The actual measurement was made perpendicular to the plane of the iris to reflect the distance from the corneal surface to the surface of the retina in the macular region (Fig. 1). Prior to 2011, images were acquired with a multipurpose ultrasound system (ATL/Philips Medical Systems, WA, USA). Beginning in 2012, images were acquired with the Vivid Q ultrasound system (General Electric, USA). Analysis was completed using the Synapse Cardiovascular DICOM analysis software tool (Fujifilm, USA).

Figure 1: Ultrasound Measurement Locations



OCT measurements of the eye were collected on flight days 30, 90, and R-30 (±7 days). These measurements include Retinal Nerve Fiber Layer Thickness (rNFL), measured using the circle scan, Total Retinal Thickness at 0-250µ from the center of the optic nerve (TRT), and Minimum Rim Width (MRW) are assessed using the radial scan (Fig. 2).

Figure 2: OCT Scan Protocol

Scan	Image	Placement	Size
Circle (rNFL)	○	Over Disc	12°
Radial	✳	Over Disc	20°
Macula	|||||||	Over Fovea	20 x 20°
Line	／	Tilt line through center of fovea and disc	30°
Vertical	|||||||	PMB b/n edge of disc and fovea	20 x 10°
Disc	☰	Over Disc	20 x 20°

CO_2 measurements were pulled directly from Operation Data Reduction Complex for the Lab and Node 3 Major Constituent Analyzers on ISS in the years 2013 to 2016. CO_2 concentrations were recorded approximately every six or seven minutes.

CO_2 measures between ultrasounds were cleaned and summarized using standard time series class metrics in MATLAB including mean, standard deviation, variance, median, interquartile range, maximum, and minimum. Regression analyses were used to quantify relationships between each of the CO_2 metrics and ultrasound and OCT measures. Generalized estimating equations adjusted for the repeated measures between individuals and demographic variables were included (age, sex, time spent in microgravity, flight day number, eye, and preflight measures for ultrasound). Adjustments for multiple comparisons were not made due to the exploratory nature of the analysis. Table 1 describes the characteristics of the ISS United States On-Orbit Segment (USOS) crewmembers.

Table 1: Characteristics of Crewmembers Evaluated

Variables	Ultrasound	OCT
Males, n (%)	17 (81%)	9 (90%)
Females, n (%)	4 (19%)	1 (10%)
Age at test, in years (mean ± SD)	48.43 ± 4.83	48.40 ± 5.12
Flight days between tests (mean ± SD)	51.37 ± 30.09	50.93 ± 22.78
Number of tests per crewmember (mean, range)	2.57 (1,6)	2.80 (1,4)

Results

CO_2 level readings on ISS are shown in Figure 3. Average CO_2 readings were taken between each test, except in the instances between launch to the first exam. This preliminary analyses showed possible associations between variability measures of CO_2 and Global rNFL, AP diameter (Fig. 4), and average CO_2 exposure with ONSD (Fig. 5). An inverse association is seen between CO_2 variability and Global rNFL. As average CO_2 variability increased, Global rNFL decreased (not shown).

Figure 3: CO_2 Level Readings on ISS

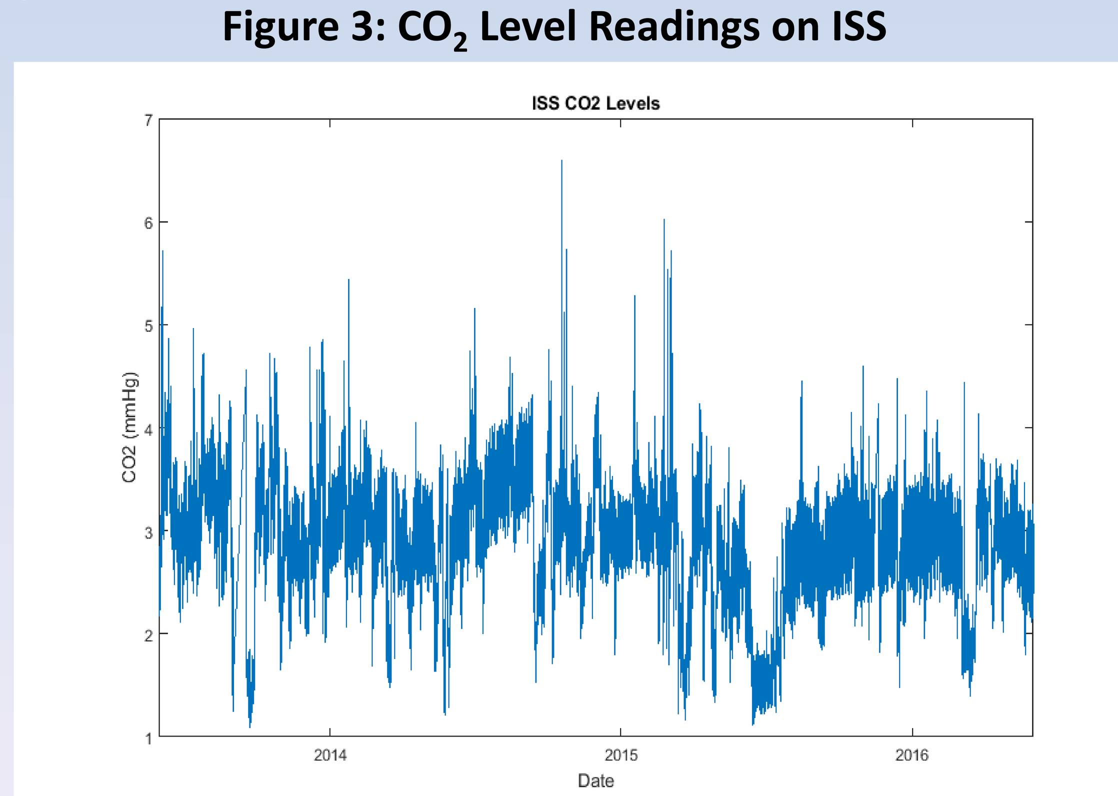
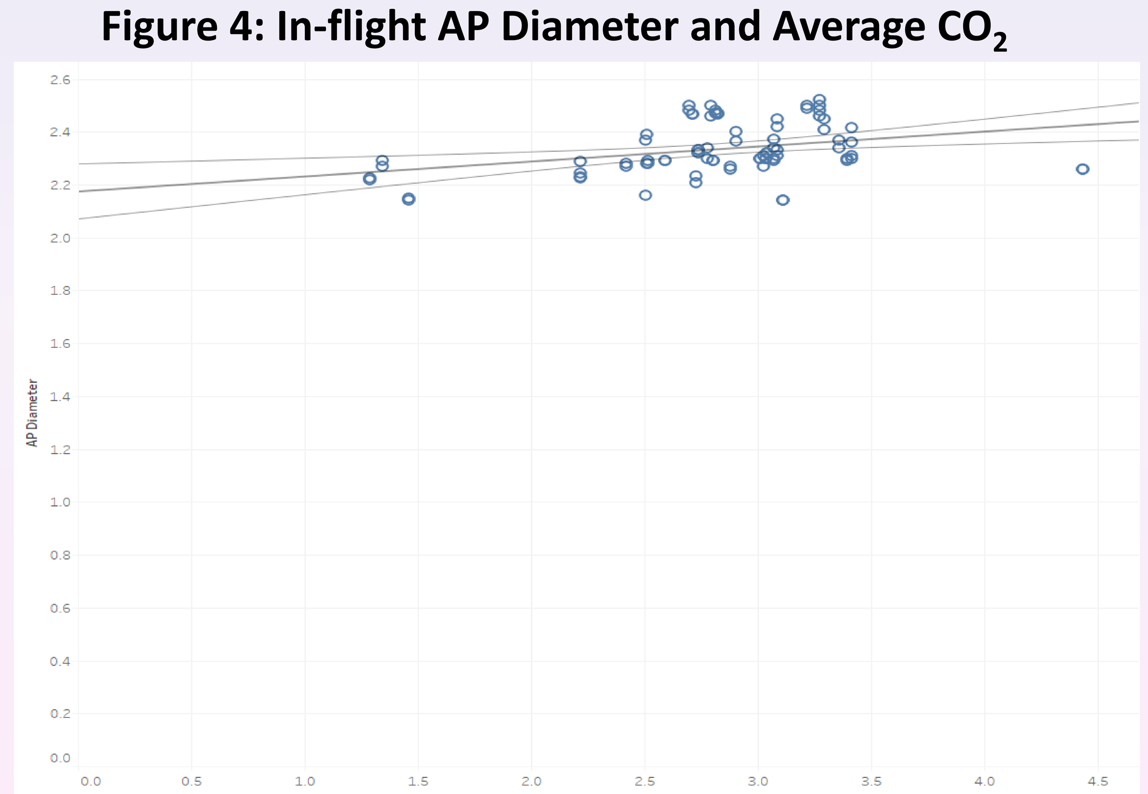
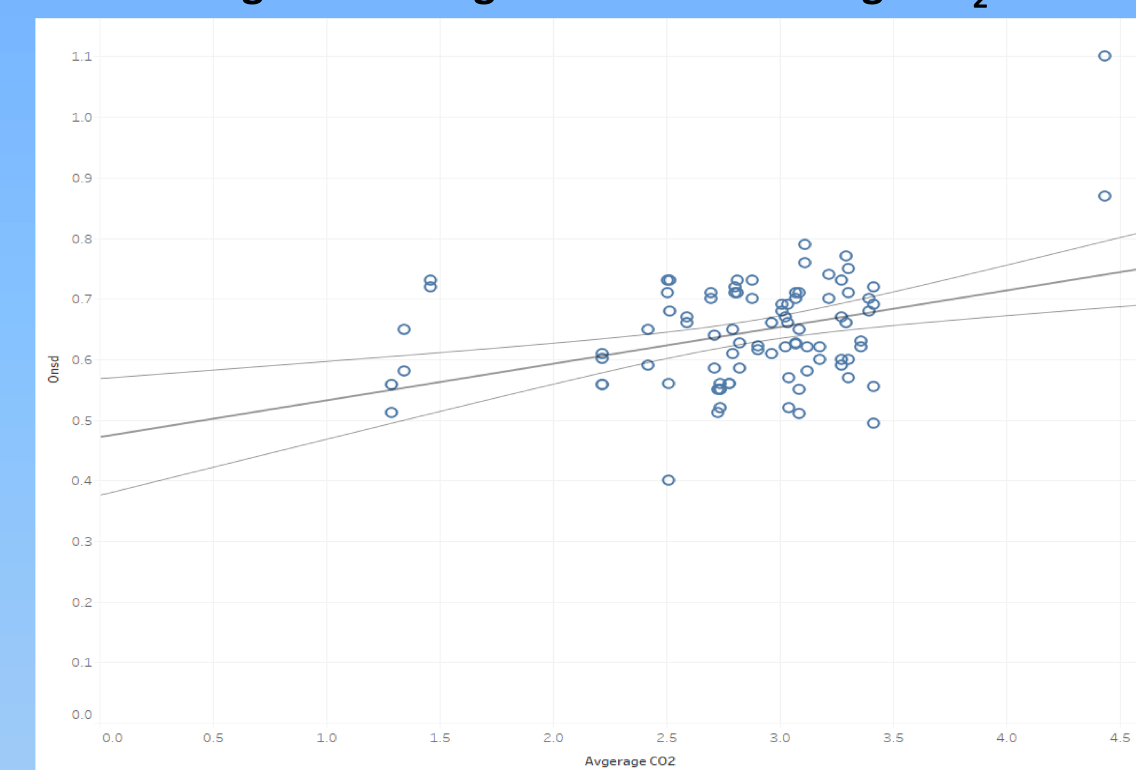


Figure 4: In-flight AP Diameter and Average CO_2



A similar association is seen between CO_2 variability and AP diameter and ONSD measurements. As average CO_2 variability increased, AP diameter and OSND increased.

Figure 5: In-flight ONSD and Average CO_2



Discussion

Possible mechanism for the association between CO_2 variability and increase in AP diameter includes choroidal expansion, which can push the retina backwards. Our analysis also shows that ONSD increases with higher average CO_2. However, acute ONSD changes can occur rapidly when exposed to CO_2.

In this exploratory analysis, the higher CO_2 mean levels associated with larger ONSD suggests a relationship between CO_2 and increased ICP. Increased CO_2 showed an association with small decreases in AP diameter, and a decrease in rNFL. Due to the exploratory nature of this analysis and the limited evidence of the physiological responsiveness of these tissues, any clinical conclusion would be preliminary.

Future work includes exploring the CO_2 readings at a more granular level for more clinical outcomes and variables (e.g., tortuosity, choroid thickness, Doppler hemodynamics). If the periods where CO_2 sensor errors occur are correlated with outcome measurements, results may be confounded. It may be beneficial to include other CO_2 metrics (e.g., use CO_2 concentrations within a smaller period for each variable). Focusing on smaller time frames closer to exams may be more appropriate to better characterize the CO_2 relationship to changes in these eye structures if the acute response to changing CO_2 levels is greater in the eye compared to a more subtle change due to long term CO_2 exposure.

Limitations

Because ultrasounds and OCT were not conducted on ISS until 2009 and 2013, respectively, only 21 subjects for ultrasound and 10 for OCT were used in the analysis. Future analyses should be expanded to include pre-flight OCT eye measurements as a baseline variable predictor to evaluate whether there are actual changes in eye physiology.