**Development of Non-invasive Method for Cerebrovascular Regulation Assessment**

Miller, S.[1], Richmond, I.[2], Borgos, J.[2], and Mitra, K.[1]
[1]Florida Institute of Technology, Melbourne, FL. [2]Brain Check Medical LLC, Shoreview, MN.

**Introduction:** Mechanisms of mild traumatic brain injury (mTBI), or concussion, are poorly understood, and non-invasive, accurate devices for early mTBI detection are lacking. Real-time identification of cerebral blood flow (CBF) dysregulation may aid in early mTBI detection. Hypercapnia is known to produce cerebrovascular vasodilation, and $CO_2$-inhalation-based hypercapnic breathing challenges have been used to study cardiovascular and respiratory dynamics. Near infrared spectroscopy (NIRS) has been used to monitor cerebrovascular function during surgery and ventilation, and cerebral bioimpedance coupled with continuous blood pressure recordings has been used to monitor CBF. These three techniques are not known to have been previously combined to use $CO_2$-inhalation-based hypercapnic breathing challenges as a tool to simulate CBF dysregulation and to monitor the CBF autoregulatory response using NIRS and bioimpedance. A breathing circuit for the selective administration of $CO_2$-compressed air mixtures was designed and tested in order to assess CBF regulatory responses to hypercapnia in healthy young adults using this combination of non-invasive methods and real-time sensors.

**Materials and Methods:** The study had Florida Institute of Technology (FIT) Institutional Research Board approval. Honeywell North 5500 series half-mask respirators were modified with in-house 3D printed connectors to securely fit two lengths of continuous positive airway pressure (CPAP) tubing and serve as the basis of the breathing circuit. Hypercapnic challenges were delivered by inserting a plug into the room air side of the breathing circuit, switching the inhalation source to a $CO_2$-compressed air mixed gas cylinder connected to a SCUBA regulator adjusted to free-float conditions. After a 5 or 10 minute baseline period, 1 to 3 hypercapnic challenges of 5 or 10 minutes duration were delivered in each study, for a total of 89 challenges in 33 studies on 26 healthy student subjects. The room air end of the breathing circuit was unplugged after each hypercapnic challenge for 5 or 10 minute recovery periods. Throughout the duration of each study, regional cerebral oxygen saturation ($rSO_2$, %) was monitored with a Nonin Equanox Advance 7600 and 8004CA NIRS sensor, partial pressure of end tidal $CO_2$ ($PCO_2$, mmHg) and respiration rate were monitored with a Smiths Medical Capnocheck II 8400, vital signs were monitored with a Bionet BM3, and bioimpedance was monitored with a UFI RESP1 impedance pneumograph and the signal digitized with a DATAQ DI-155.

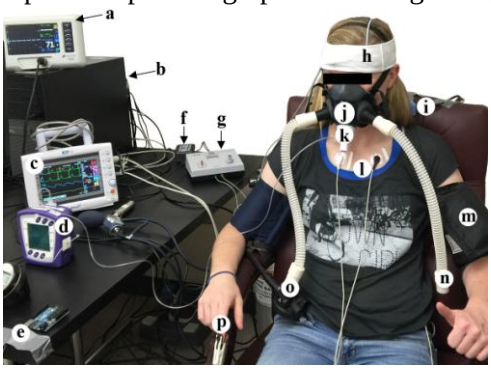


**Figure 1. Subject fully connected to breathing and monitoring circuit.** a. Nonin Equanox Advance 7600, b. Data acquisition computer, c. Bionet BM3, d. Smiths Medical Capnocheck II 8400, e. Arduino Uno, f. DATAQ Instruments Model DI-155, g. UFI Model RESP1, h. Nonin Equanox Advance 8004CA sensor and bioimpedance electrodes under cotton headband, i. Nonin Equanox Advance 7600PA, j. Modified North 5500 half-mask respirator, k. Smiths Medical airway adaptor/sample line, l. ECG leads and electrodes, m. Blood pressure cuff, n. Room air end of circuit: CPAP tubing and rubber plug, o. $CO_2$-compressed air mixed gas delivery end of circuit: SUBGEAR SG 100 and CPAP tubing, p. Pulse oximeter.

**Results and Discussion:** Disruption of the Equanox Advance 7600 data output connection ($rSO_2$) excluded 7 challenges from further analysis, and a total of 82 challenges in 31 studies were analyzed in detail. Change in $PCO_2$ ($\Delta PCO_2$) during $CO_2$ inhalation provided a measure of the degree of hypercapnic challenge. Change in $rSO_2$ ($\Delta rSO_2$) during hypercapnia was positively correlated to $\Delta PCO_2$ ($R^2 = 0.40$). The mean response ± standard error in $\Delta PCO_2$ and $\Delta rSO_2$ were 6.39 ± 0.52 mm Hg and 2.22 ± 0.30 % respectively. In the 5 subjects studied for intra-subject reproducibility assessment, the mean inter-day $\Delta PCO_2$ change was 1.52 mm Hg, and mean inter-day $\Delta rSO_2$ change was 1.62%. Individual analysis of vital signs (respiration and heart rate and variance) and bioimpedance changes in each of the 31 studies was required to identify the combined measured response to hypercapnia in each study.

**Conclusions:** The combined monitoring of vital signs, bioimpedance, and changes in $rSO_2$ can detect periods of hypercapnia, which alter CBF, better than $rSO_2$ alone. Algorithms will be developed to relate $\Delta rSO_2$ and vital sign changes and trends during hypercapnia to enable non-invasive detection of CBF dysregulation, which may be a marker of mTBI. The non-invasive method of cerebrovascular regulation assessment will be extended to study concussed and non-concussed athletes at FIT and combined with cognitive data through a partnership with the Psychology Department and Athletic Program.

**Acknowledgements:** This research was funded by NSF CBET Grant 143551.