CEREBRAL HYPOPERFUSION PRECEDES NAUSEA DURING CENTRIFUGATION

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RUNNING HEAD: CEREBRAL HYPOPERFUSION PRECEDES NAUSEA

Word Count
Abstract: 244 words
Narrative: 2879 words
References: 15
Tables: 0
Figures: 4
ABSTRACT

Nausea and motion sickness are important operational concerns for aviators and astronauts. Understanding underlying mechanisms associated with motion sickness may lead to new treatments. The goal of this work was to determine if cerebral blood flow changes precede the development of nausea in motion sick susceptible subjects. Cerebral flow velocity in the middle cerebral artery (transcranial Doppler), blood pressure (Finapres) and end-tidal CO₂ were measured while subjects were rotated on a centrifuge (250°/sec). Following 5 min of rotation, subjects were translated 0.504 m off-center, creating a +1Gx centripetal acceleration in the nasal-occipital plane. Ten subjects completed the protocol without symptoms while 5 developed nausea (4 while off-center and 1 while rotating on-center). Prior to nausea, subjects had significant increases in blood pressure (+13±3 mmHg, P<0.05) and cerebrovascular resistance (+46±17%, P<0.05) and decreases in cerebral flow velocity both in the second (-13±4%) and last minute (-22±5%) before symptoms (P<0.05). In comparison, controls demonstrated no change in blood pressure or cerebrovascular resistance in the last minute of off-center rotation and only a 7±2% decrease in cerebral flow velocity. All subjects had significant hypocapnia (-3.8±0.4 mmHg, P<0.05), however this hypocapnia could not fully explain the cerebral hypoperfusion associated with the development of nausea. These data indicate that reductions in cerebral blood flow precede the development of nausea.

Further work is necessary to determine what role cerebral hypoperfusion plays in motion sickness and whether cerebral hypoperfusion can be used to predict the development of nausea in susceptible individuals.

KEYWORDS: Cerebral Blood Flow, Vestibular, Hypergravity, Cerebrovasculature
INTRODUCTION

Motion sickness is an important operational concern for both the military and NASA. Recently, we found that subjects who experienced motion sickness during parabolic flight were also more likely to have increased cerebrovascular resistance and orthostatic intolerance after such flight. (10). In another study, following parabolic flight, one subject that became nauseated also demonstrated a decrease in cerebral flow velocity and increase in cerebrovascular resistance (8). These data suggest that changes in cerebral blood flow occur concurrently with the development of nausea and motion sickness.

Since the vestibular system is necessary to develop motion sickness (2), the role of vestibular inputs in cerebral blood flow regulation must be considered. Previous work has found that activating the semicircular canals using caloric stimulation results in increases to blood flow in both the basilar (3) and middle cerebral arteries (13) as well as the parietal lobe (12) while decreasing flow in the posterior cerebral artery (13). In contrast, the role of otolith activation on the cerebrovasculature has not been as well studied. Our group recently found that subjects exposed to 30 minutes of hypergravity demonstrate impaired dynamic autoregulation that returns to normal upon the assumption of the upright posture (11). Furthermore, this impairment was found to correlate with indirect measures of otolith sensitivity. We have also examined the effect of otolith stimulation by changing head position relative to gravity while subjects were supine, with and without lower body negative pressure (14). In this work we found that stimulation of the otoliths by flexing the head forward decreased cerebrovascular resistance whereas having subjects extend their neck backwards increased cerebrovascular resistance. Thus,
previous data suggest that activation of both the semi-circular canals and otoliths results in cerebral blood flow changes.

The goal of this work was to examine temporal changes in cerebral blood flow in subjects who developed nausea during selective otolith stimulation using short arm centrifugation. We hypothesized that subjects who developed nausea would demonstrate decreases in cerebral flow velocity prior to the development of symptoms.

**METHODS**

**Subjects**

Twenty-five healthy, non-smoking subjects (29±8 years, 13 females, 12 males) were recruited for a short arm centrifugation study. Ten subjects were excluded due to signal loss during centrifugation.

All subjects were screened with a medical history and had refrained from caffeine, medications (prescription or non-prescription) or exercise for 12 hours prior to testing and were at least 2 hours postprandial at time of testing. The study protocol was approved in advance by the Legacy Health Systems Institutional Review Board. Each subject provided written informed consent before participating.

**Experimental Protocol**

**Instrumentation**

Each subject was instrumented with a photoplethysmographic cuff on the middle finger of the left hand slung at the level of the right atrium to obtain non-invasive beat-by-beat blood pressure (Finapres, Ohmeda, CO, USA). End-tidal CO₂ was monitored by
sampling expired air via a nasal catheter (Puritan-Bennett, Wilmington, MA). The middle cerebral artery was insonated by placing a 2-Mhz Doppler probe (MultiDop T, DWL, Germany) over the temporal window to measure blood flow velocity as described by Aaslid et al. (1). The envelope of the velocity waveform was derived from the FFT of the Doppler signal. All physiologic signals were digitized at 500 Hz using a commercially available digitizer (Windaq, Dataq Instruments, OH, USA) and stored on a computer for offline analysis.

To assess cerebrovascular reactivity, just prior to centrifugation, subjects were asked to breathe normally for 3 min while resting seated upright on the centrifuge. They were then given an inspired gas mixture of 8% CO2, 21% O2 and balance nitrogen for 2 min. Following this subjects were asked to mildly hyperventilate for 2 min.

Centrifugation Protocol

Subjects were seated upright over the center of rotation on a short-arm centrifuge device driven by direct-drive motor (80 ft lb) that contained bearing assemblies allowing asymmetric loads. Subjects were restrained so as to minimize motion of their torso, legs and head during centrifugation. A snug five-point safety harness, and vacuum forming cushions, restrained the subject as comfortably as possible. All centrifugation was performed in the dark to eliminate visual cues of orientation relative to gravity.

The centrifugation protocol was performed as follows:

1) 5 min of resting quietly in the dark

2) Acceleration at 25°/s² to 250°/sec over center of rotation for 5 min

3) Translate chair 5 cm/s until 0.504 m off center for 5 min (See Fig. 1)
4) Return to center of rotation for 5 min

5) Translate in opposite direction for 5 min

6) Return to center of rotation for 5 min

7) Decelerate to complete stop at $25^\circ/s^2$

Subjects that developed symptoms of nausea were returned to center, if off-center, and decelerated immediately. Subjects were positioned so that centripetal acceleration was directed along the nasal-occipital axis (i.e. pitch plane).

Data processing and Analysis

Post-processing was done using custom-written MATLAB scripts (The 'Mathworks, Natick, MA). Mean values for blood pressure and cerebral blood flow velocity were determined from the associated beat-by-beat waveforms. Blood pressure was hydrostatically corrected to heart and brain level. End tidal CO$_2$ was determined from the breath-by-breath expired CO$_2$ waveform. Cerebrovascular resistance was calculated from brain level blood pressure and cerebral flow velocity. Cerebrovascular reactivity was determined by a linear fit of beat-by-beat cerebral flow velocity with associated end-tidal CO$_2$ values after incorporating the known 6 sec time delay between end-tidal CO$_2$ changes and associated cerebral flow velocity response. (7) The effects of centrifugation (no rotation vs. rotation over center vs. rotation off-center) or motion sickness susceptibility (controls vs. subjects that developed nausea) on cerebral flow velocity, arterial pressure, end tidal CO$_2$, and cerebrovascular resistance were assessed using a repeated-measures two-way ANOVA, respectively, with a post-hoc Bonferroni
test for multiple comparisons. Data are presented as mean±SEM and levels of p<0.05 are considered statistically significant.

RESULTS

Development of Motion Sickness

Of fifteen subjects, 10 were able to complete the protocol (6 females, 4 males) while 5 developed nausea and had to terminate before completion (2 females, 3 males). Of the subjects that terminated 4 developed symptoms while rotating off-center facing forward (i.e. perceived as a pitch forward) and one during rotation over center. Since 80% of the affected subjects developed motion sickness in the pitch forward position, comparisons were made between the 5 min of pitch forward in the control group and the last 5 min prior to the development of nausea in the motion sick susceptible group.

Cerebrovascular Reactivity

Analysis of the linear relationship between cerebral flow velocity and end tidal CO₂ produced similar results for all subjects. The control subjects had a cerebrovascular reactivity of 2.5±0.1 %/mmHg with an r² of 0.80±0.03 while the subjects that developed nausea had values of 2.4±0.2 %/mmHg with an r² of 0.85±0.03.

Cerebrovascular Response to Centrifugation

Figure 2 (left panel) demonstrates a typical response for a control subject during centrifugation. Cerebral flow velocity remained unchanged while the subject was rotating on center of axis, decreased slightly during pitch forward and increased slightly during
pitch backward. Both rotation on center and off-center were associated with a slight increase in blood pressure. Finally translation forward caused a reduction in end-tidal CO₂. The right panel demonstrates a typical response from a subject that developed nausea after 212 sec in the pitch forward position. Prior to the development of nausea there was a steady decrease in cerebral flow velocity. Concurrent with this, blood pressure increased while end-tidal CO₂ decreased.

Neither controls nor motion sick subjects had significant changes in cerebral flow velocity, blood pressure or end-tidal CO₂ with rotation on center (Fig. 3). However, the motion sick subjects demonstrated a ~20% increase in cerebrovascular resistance.

Cerebrovascular Response Prior to Nausea

Upon moving the control subjects from center of rotation to 0.504 m off-center, while facing away from center of rotation, there was a slight decrease in cerebral flow velocity that became significant in the 4th and 5th minutes (Fig. 3, P<0.05). However, this decrease was not associated with any change in cerebrovascular resistance or blood pressure. It was concurrent with lower end-tidal CO₂ values (P<0.05).

In the motion sick subjects, during the last five minutes prior to the development of nausea, a similar trend was observed in cerebral flow velocity but with decreases significantly greater than those observed in controls in the 5th minute (P<0.05) becoming significant in the last two minutes prior to symptom development. Subjects that developed nausea also had greatly elevated cerebrovascular resistance during the 5 minutes prior to symptoms, associated with an increase in blood pressure that returned to baseline levels in the last minute prior to symptoms.
Both groups demonstrated a reduction in end tidal CO₂, both during the 5 min of pitch forward or prior to nausea. While hypocapnia occurred concurrently with reductions in cerebral flow velocity, end tidal CO₂ was not significantly different between groups at any point. In contrast, decreases in cerebral flow velocity were significantly greater in the last minute prior to the development of nausea in motion sick subjects than in controls in the last minute of pitch forward centrifugation.

Further examination of the 240 seconds prior to development of symptoms in the motion sick group demonstrates several important temporal patterns (Fig. 4). While cerebral flow velocity decreased to significantly below baseline values starting ~120 seconds prior to symptom development, this cerebral hypoperfusion was preceded by a cerebral vasoconstriction which began ~210 sec prior to the development of nausea. This increase in cerebrovascular resistance was likely not the result of an autoregulatory response to increasing pressure since blood pressure remained stable, above baseline levels, over the period of 210-60 seconds prior to symptoms. In fact, blood pressure declined in the last minute prior to nausea while cerebrovascular resistance continued to remain elevated, likely worsening the cerebral hypoperfusion that was already present.

Reductions in end tidal CO₂ also began to develop ~200 sec prior to symptom development. This hypocapnia likely contributed to the increase in cerebrovascular resistance during the same period. However, while end tidal CO2 was significantly lower than baseline levels by 3 min prior to nausea, it did not significantly change from 3 min prior until the development of nausea. While non significant end-tidal CO₂ decreased – 0.5 ± 0.7 mmHg between the second last and last minute prior to symptoms while cerebral flow velocity fell 9 ± 3 %.
DISCUSSION

This study provides three main findings. First, reductions in cerebral flow velocity precede the development of nausea in those susceptible to motion sickness during centrifugation. Second, this hypoperfusion is associated with a cerebral vasoconstriction that is independent of blood pressure changes. Third, reductions in end-tidal CO₂ may contribute to but do not fully explain this cerebral hypoperfusion.

Our finding that cerebral hypoperfusion and vasoconstriction are associated with the development of nausea is consistent with our previous finding that a subject who developed nausea during post parabolic flight tilt table testing demonstrated decreased cerebral flow velocity and increased cerebrovascular resistance (8). Since previous work has demonstrated that an intact vestibular system is necessary to develop motion sickness (2), a role for vestibular inputs in this cerebral hypoperfusion seems likely.

We have previously found that stimulation of the vestibular system through parabolic flight (8, 10) or hypergravity (11) results in changes in the cerebral blood flow response to an upright tilt table test. Similarly, otolith stimulation using static head rotations results in changes in cerebral flow velocity and cerebrovascular resistance (14).

Our finding that increases in cerebrovascular resistance and reductions in cerebral flow velocity precede the development of symptoms of nausea suggest that reductions in cerebral blood flow may be integral in the development of motion sickness. Interestingly, this cerebral hypoperfusion occurred in the face of increased brain level blood pressure. While control subjects did not demonstrate a significant change in blood pressure during centrifugation, motion sick subjects had a slight but non-significant increase while
rotating on-center and a significant increase in blood pressure prior to the development of symptoms. Motion sick subjects also had a significant increase in cerebrovascular resistance throughout centrifugation. A possible cause of this increase in cerebrovascular resistance is a normal autoregulatory response.

Cerebral autoregulation works to maintain cerebral blood flow constant by adjusting cerebrovascular resistance in response to changing perfusion pressure (6). Thus increases in blood pressure should result in vasoconstriction to maintain cerebral blood flow relatively constant. While an autoregulatory response likely explains the increase in cerebrovascular resistance while rotating over center of rotation (i.e. cerebrovascular resistance increased in response to increased blood pressure without changing cerebral blood flow), the increase in cerebrovascular resistance prior to the development of nausea appears maladaptive since resistance continued to increase even when blood pressure and cerebral blood flow were decreasing (Fig. 3). These data suggest that either cerebral autoregulation was impaired immediately prior to symptom development or another mechanism was causing an overriding vasoconstriction.

One possible mechanism that could explain the increase in cerebrovascular resistance and reduction in cerebral flow velocity is the development of hypocapnia. Reductions in arterial CO₂ are known to act as a potent cerebral vasoconstrictor (6). The development of nausea is often associated with significant anxiety, and thus it is possible that subjects began to hyperventilate, causing significant hypocapnia. However, it is unlikely that hyperventilation associated with anxiety was the sole reason for increased cerebrovascular resistance because hypocapnia occurred prior to the development of
symptoms in the motion sick subjects. In addition, control subjects developed similar levels of hypocapnia without any symptoms of motion sickness or signs of anxiety.

Since both groups were experiencing direct vestibular stimulation, it is plausible that a vestibulorespiratory mechanism was activated. Previous work in animals has shown that stimulation of the vestibular system can change respiration through a brainstem mediated mechanism (15). Because hypocapnia unassociated with nausea was present during the entire 5 minutes of off-center rotation (i.e. otolith stimulation, see Fig. 1) in the control group and because hypocapnia was not present in either group during on-center rotation (minimal otolith stimulation), a more direct vestibulorespiratory mechanism for hypocapnia seems likely.

Regardless of the mechanism, hypocapnia in and of itself could cause significant cerebral hypoperfusion. While vestibular mediated hypocapnia likely contributed to reductions in cerebral flow velocity and increases in cerebrovascular resistance, it did not appear to be the primary mechanism. Two lines of evidence suggest that hypocapnia may not have been the primary mechanism contributing to cerebral hypoperfusion. First, levels of hypocapnia were similar between motion sick and control groups, while cerebral hypoperfusion was significantly greater in the motion sick subjects. Second, decreases in cerebral flow velocity were greatest from the second to last minute prior to symptom development (-9 ± 3%) while reductions in end-tidal CO₂ were minimal (-0.5 ± 0.7 mmHg). Using individual motion sick subjects' cerebrovascular reactivity to estimate the change in cerebral flow velocity due to end tidal CO₂ changes during the last two minutes prior to nausea development, the predicted decrease is only -1.5% (Range +2.3 to -5.6%), compared to the 9% decrease seen in motion sick subjects from the second to last
minute prior to nausea. Thus, it appears that the cerebral hypoperfusion preceding the development of nausea was at least partially independent of hypocapnia.

One limitation of the transcranial Doppler methodology used in our study is that cerebral blood velocity rather than flow is measured. For velocity changes to be equivalent to flow changes, arterial diameter at the point of insonation must remain constant. Recent measures of middle cerebral artery diameter by MRI combined with transcranial Doppler assessment of cerebral flow velocity have demonstrated that diameter at the insonation point does not change despite large changes in cerebral flow velocity elicited by stimuli such as lower body negative pressure and changes in end tidal CO₂ (9). Other work has examined the lower limit of cerebral autoregulation using a combination of ganglionic blockade and lower body negative pressure to induce hypotension. These studies showed significant correlations between cerebral blood flow (using ¹³³Xe) and cerebral flow velocity, r²=0.60 (4) and r²=0.73 (5), further supporting the view that changes in cerebrovascular tone occur downstream from the arterial segment used for transcranial Doppler measures. Thus, it appears that changes in cerebral flow velocity proportionally reflect changes in cerebral blood flow.

**Summary**

Nausea induced by centripetal acceleration is preceded by reductions in cerebral blood flow and increases in cerebrovascular resistance. This cerebral hypoperfusion does not appear to be the result of increased blood pressure nor is it entirely explained by reductions in end tidal CO₂ during centrifugation. While it is likely that a vestibular mediated cerebral vasoconstriction precedes the development of nausea, further work in
necessary to determine the mechanism of the vasoconstriction. Our data suggest that reductions in cerebral flow velocity may be used to predict the development of nausea in motion sick susceptible individuals. If reductions in cerebral blood flow are integral to motion sickness, future preventative strategies could employ the use of inspired CO₂ or other cerebral vasodilators to prevent the development of nausea. Future work is required to examine whether the maintenance of cerebral flow helps to postpone the development of nausea in motion sick susceptible individuals.

ACKNOWLEDGEMENTS

The authors would like to thank Valerie Stallings, Tom Bennett, Patty Cunnigham, Sue Peznecker and Sarah Goodell for their assistance in data collection.

GRANTS

This work was supported by NIDCD grants R03DC005545 (Serrador), R03DC005547 (Wood), R01DC000205 (Black) and a NASA-sponsored Presidential Early Career Award (Schlegel).

REFERENCES


2. Graybiel A, Johnson WH. A comparison of the symptomatology experienced by healthy persons and subjects with loss of labyrinthine function when exposed to unusual


Figure Legends

Figure 1 – Diagrammatic representation of centrifuge protocol. Subjects were first rotated with head over center of rotation for 5 min (250 deg/s). Following this, the centrifuge chair moved along a track (0.05 m/s) until the subject’s head was 0.504 m off-center of rotation. Subjects would remain in this position for 5 min (perceived as a 45° forward tilt in the pitch plane). Following this subjects were returned to center for 5 min before moving to the other end of the centrifuge arm (perceived as 45° backward pitch) for another 5 min followed by returning to center for 5 min.

Figure 2 – Representative data from control subject (left panel) demonstrating individual waveforms for cerebral flow velocity, blood pressure (corrected to heart level) and expired CO₂. Subject completed entire protocol without the development of any motion sickness symptoms. Representative data from subject susceptible to motion sickness (right panel). Subject reported nausea 812 sec into protocol. The subject was immediately returned to center of rotation and then decelerated to a stop. Symptoms resolved spontaneously within a few minutes.

Figure 3 – Mean response of control subjects (open circles, N=10) and subjects that developed nausea (filled circles, N=5) in cerebral flow velocity (CFV), cerebrovascular resistance (CVR), brain level blood pressure (BP\textsubscript{brain}), and end tidal CO₂ (P\textsubscript{ET}CO₂). Data points represent 1 min averages ± SEM. First 5 min were sitting quietly in the dark. Second five minutes were rotation over center. Last 5 min were in the pitch forward position for controls and the last 5 min before the development of nausea in motion sick
susceptible subjects. Pitch forward condition was used for comparison since 4 of the 5 subjects that developed nausea did so in the pitch forward position. * - significant difference from baseline for susceptible subjects, P<0.05; ** - significant difference from baseline for both groups, P<0.05; α - significant difference between groups, P<0.05.

Figure 4 – Changes in cerebral flow velocity (CFV), cerebrovascular resistance (CVR), brain level blood pressure (BP<sub>brain</sub>), and end tidal CO<sub>2</sub> (P<sub>ETCO<sub>2</sub></sub>) for subjects that developed symptoms of nausea (N=5). Time represents seconds before subjects reported feeling nauseated. Data points are 10 sec averages ± SEM. Solid lines represent baseline quiet resting levels. Filled circles are data points that were not significantly different from baseline. Open circles are data points that are significantly different from baseline (P<0.05).
TRANSLATION TO PITCH FORWARD
Figures (separate file for each)

- CFV (% Baseline)
- CVR (% Baseline)
- BP脑 (% Baseline)
- P脑CO₂ (mmHg)
- Radial Position (m)
- Radial Velocity (deg/s)
Figures (separate file for each)