

Predicting Motion Sickness during Parabolic Flight

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ABSTRACT

Background: There are large individual differences in susceptibility to motion sickness. Attempts to predict who will become motion sick have had limited success. In the present study we examined gender differences in resting levels of salivary amylase and total protein, cardiac interbeat intervals (R-R intervals), and a sympathovagal index and evaluated their potential to correctly classify individuals into two motion sickness severity groups. **Methods:** Sixteen subjects (10 men and 6 women) flew 4 sets of 10 parabolas aboard NASA's KC-135 aircraft. Saliva samples for amylase and total protein were collected preflight on the day of the flight and motion sickness symptoms were recorded during each parabola. Cardiovascular parameters were collected in the supine position 1-5 days prior to the flight. **Results:** There were no significant gender differences in sickness severity or any of the other variables mentioned above. Discriminant analysis using salivary amylase, R-R intervals and the sympathovagal index produced a significant Wilks' lambda coefficient of 0.36, $p=0.006$. The analysis correctly classified 87% of the subjects into the none-mild sickness or the moderate-severe sickness group. **Conclusions:** The linear combination of resting levels of salivary amylase, high frequency R-R interval levels, and a sympathovagal index may be useful in predicting motion sickness severity.

Key words: parabolic flight, amylase, R-R intervals, sympathovagal index, gender

INTRODUCTION

Motion sickness is a fairly common clinical syndrome characterized by a number of signs and symptoms including nausea, vomiting, pallor and cold sweating (Harm, 1990; Reason & Brand, 1975). It is the most clinically significant phenomenon occurring during the first few days of space flight (Reschke et al., 1994), and is one of the most important health and safety issues that may influence the advancement of virtual environment technology (Barfield & Weghorst, 1993; Kalawsky, 1993; Stanney, Salvendy, & al., 1998). Symptoms can be provoked during a wide variety of motion and perceived motion situations in labyrinthine-intact individuals. Most of the symptoms of motion sickness are mediated by the autonomic nervous system primarily via vestibulo-autonomic pathways (Yates & Miller, 1996). Early signs/symptoms such as pallor and cold sweating are associated with increased sympathetic activity, whereas severe nausea and vomiting are related to increased parasympathetic activity (Harm, 1990).

There are large individual differences with respect to susceptibility to motion sickness. Individuals' physiologic responses during motion sickness may vary as a function of the stimulus conditions and duration of exposure to motion sickness provocation. These two facts make it difficult to predict who will become ill, and under what conditions. Several studies, however, have evaluated the relationship between motion sickness susceptibility and resting levels of salivary amylase and total protein (Gordon et al., 1994; Gordon et al., 1988; Gordon et al., 1989; Gordon et al., 1992) and cardiac R-R interval variations (Graybiel, Crame, & Wood, 1981; Igarashi, Himi, Ishii, Patel, & Kulecz, 1987; Ishii, Igarashi, Patel, Himi, & Kulecz, 1987; Uijtdehaage, Stern, & Koch, 1992; Uijtdehaage, Stern, & Koch, 1993) in an effort to predict motion sickness.

Secretion of salivary amylase is regulated primarily by the sympathetic nervous system. Increased sympathetic activity is associated with higher levels of salivary amylase. Gordon and his colleagues (1994; 1992) found that resting levels of salivary amylase were significantly higher in individuals susceptible to seasickness than in those who were nonsusceptible. Those authors suggested that their findings indicate that seasickness susceptible individuals may have higher resting levels of sympathetic activity than nonsusceptible subjects. Salivary total protein was found to be significantly higher in moderately or severely sick subjects during coriolis sickness compared to a control condition (Gordon et al., 1988), and was significantly correlated with seasickness severity (Gordon et al., 1989).

High frequency oscillations (0.20-0.30 Hz) of cardiac R-R intervals, also referred to as respiratory sinus arrhythmia (RSA), are modulated almost exclusively by the parasympathetic nervous system. Higher levels of parasympathetic modulation are associated with greater R-R variability in the RSA frequency band (Akselrod et al., 1981; Hedman, Hartikainen, Tahvanainen, & Hakumaki, 1995). The potential utility of cardiac variability as a measure of motion sickness severity was demonstrated in squirrel monkeys (Igarashi et al., 1987; Ishii et al., 1987), where increased cardiac variability was related positively to symptom severity. In studies using a circularvection drum to induce motion sickness symptoms, Uijtdehaage et al. (1992) observed decreases in RSA during drum exposure. In addition, they found that increased fluctuations in vagal-cardiac nerve traffic (higher levels of RSA) prior to drum rotation predicted a low incidence of motion sickness symptoms. In a subsequent study, these investigators found that RSA level prior to drum rotation correctly predicted sickness level during the test in 76.7% of the subjects (significantly better than chance) with higher levels of high frequency R-R interval variability predicting fewer symptoms (Uijtdehaage et al., 1993).

Taken together, these findings suggest that individuals with higher resting sympathetic activity may be more susceptible, and those with higher resting parasympathetic oscillatory activity may be less susceptible to motion sickness. In addition, these observations raise the possibility that salivary amylase (as an indicator of sympathetic activity) and high frequency R-R interval variability (as an indicator of parasympathetic oscillations) may be useful predictors of motion sickness susceptibility. Moreover, the combination of resting salivary amylase levels and RSA may have greater predictive power than either measure alone.

The primary purpose of the present investigation was to determine whether or not resting salivary amylase, salivary total protein and/or resting RSA could be useful predictors of motion sickness susceptibility to parabolic flight. In addition, we examined gender differences in motion sickness severity, resting amylase and total protein, and RSA.

MATERIALS AND METHODS

Subjects

Sixteen healthy nonsmoking normotensive test subjects (ten men and six women, mean age 32.25 years, range 22-45 years) were recruited for parabolic flight on NASA's KC-135 aircraft. All subjects passed a physiologic training course and gave written consent prior to participation in the protocol, which was approved by the Johnson Space Center Institutional Review Board. Selection of subjects was based on a screening evaluation that included a detailed medical history, physical examination, complete blood count, blood chemistry analysis, urinalysis, resting electrocardiogram, and drug screen. Caffeine, alcohol, heavy exercise and all medications (including anti-motion

sickness medications), were strictly prohibited beginning 24 hours prior to any testing, which began in the morning hours. All subjects were instructed to eat a low-calorie, low-fat, high-complex carbohydrate breakfast on testing days prior to actual testing.

Procedures

The data presented here derive from a larger study designed to assess the relationships between autonomic cardiovascular function, orthostatic tolerance and motion sickness (Schlegel et al., 2001). Therefore, only those procedures relevant to the present paper are described here. Testing was conducted at a room in NASA's hanger facility at Ellington Air Field, Pasadena, TX where the temperature and relative humidity were controlled within the ranges, respectively, of 22-24° C and 40-50%. Preflight testing occurred 1-5 days prior to the flight in the following sequence: 1) ambulation to the testing area; 2) instrumentation for measurement of cardiovascular parameters (as described below); 3) supine rest for 15 min; and 4) supine controlled breathing at 0.25 Hz for 5 min, or until 256 consecutive heart beats and beat-to-beat arterial pressures were recorded for subsequent spectral analysis. Saliva samples were recorded preflight the day of the flight and motion sickness symptoms were collected during the flight (as described below).

Parabolic Flight Protocol: While loosely restrained at the waist, subjects flew 4 sets of 10 parabolas in the seated position aboard NASA's KC-135 aircraft, a Boeing 707 specifically modified for parabolic flight. During their flights, subjects were instructed to avoid unnecessary head movements by looking forward at a monitor-sized target placed ~ 1.5 m in front of them. As verified by an accelerometer mounted inside the aircraft, single parabolas consisted of the following three phases, each lasting ~ 20-25 s: 1) "pull-up" with increased G-load of up to +1.8 G_z; 2) microgravity (~ 0.01 G_z); and 3) "pull-out" with increased G-load of up to + 1.8 G_z.

Salivary Amylase and Total Protein: Salivary samples for amylase and total protein were collected preflight by having subjects suck on a standard cotton salivette (Sarstedt, Inc.) for three minutes. Samples were collected at least one hour after the last consumption of solids or liquids (the morning of the flight), and after having subjects rinse their mouths with tap water prior to the beginning of the collection. After collection, the cotton was placed back in its container top, which has small perforations in it to allow liquid saliva to drain out of the cotton swab. The tubes were later centrifuged at 3000 rpm for 10 minutes and the liquid separated into a screw top cry tube. Since saliva has a much higher amylase level than serum, the sample was diluted 1:200 using a commercial dilution device (Hamilton Micro Lab 900). The diluted sample was then placed on a Beckman CX5 Chemistry Analyzer programmed for serum amylase analyses.

Total protein content of the saliva sample was measured using the commercially available BCA protein assay (Pierce Biochemicals, Inc., Rockford, IL). The centrifuged saliva was diluted 1:10 with ddH₂O and 10 ul samples were dispensed into a 96-well microtiter plate and assayed for total protein using the BCA kit. Total protein was determined by comparison to a standard curve (i.e., purified bovine serum albumin in ddH₂O) constructed on the same plate and expressed as total protein (ug)/(ml) of saliva.

R-R interval and Arterial Pressure Responses during Controlled Frequency Breathing: Subjects were instrumented with: 1) electrocardiographic leads and electrodes (including an electrode for impedance measurements of abdominal-muscle respiratory excursions (Physio-Control, Redmond, WA); 2) a nasal probe for measurement of end-tidal CO₂ (Puritan-Bennett, Wilmington, MA); and 3) a finger

photoplethysmographic device (Finapres 2300, Ohmeda, Englewood, CO) for beat-to-beat estimates of blood pressure (BP). Prior to preflight testing, subjects first chose a comfortable respiratory excursion (tidal volume) and practiced breathing to the metronome at that excursion. They were then asked to use this same excursion throughout the 5 min period of controlled frequency breathing. During data collection itself, based upon our observation of end-tidal CO₂ levels and of abdominal and nasal respiratory movements and tracings, we also provided verbal feedback to the subjects as necessary to ensure that they were maintaining gross consistency in respiration. The continuous cardiovascular signals from these devices were digitally recorded.

Spectral powers were derived from the 5-min series of consecutive R-R intervals, systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) collected in the supine position during metronome-controlled breathing (Brown, Beightol, Koh, & Eckberg, 1993) at 0.25 Hz. The R-R interval and arterial pressure power spectra were computed in the band from 0 to 4.0 Hz. Very low and low frequency fluctuations in R-R intervals (i.e., peaks at 0.04 and 0.10-0.12 Hz, respectively) are believed to be jointly mediated by the sympathetic and parasympathetic nervous systems, whereas higher (i.e., respiratory) frequency fluctuations are mediated solely by the parasympathetic nervous system (Akselrod et al., 1985; Brown et al., 1993; Koh, Brown, Beightol, Ha, & Eckberg, 1994; Pomeranz et al., 1985). Changes in the relative sizes of these peaks, especially during controlled frequency breathing (Brown et al., 1993), can be used to estimate relative changes in sympathetic and parasympathetic modulation (Koh et al., 1994; Pomeranz et al., 1985), and to calculate a presumptive cardiovascular sympathovagal index (Novak, Novak, Opfer-Gehrking, O'Brien, & Low, 1998). The sympathovagal index (SVI) was defined as the ratio of the low frequency SBP spectral power and the high frequency R-R interval power.

For spectral analyses, the Welch algorithm for averaging periodograms (Ito & Honjo, 1990) was used in accordance with the method of Rabiner et al. (1979). Specifically, the continuous series of R-R intervals, SBPs or DBPs was fitted to a cubic spline function, interpolated at 8 Hz to obtain equidistant time intervals, and divided into seven equal overlapping segments. Segments were then de-trended, Hanning window filtered, fast-Fourier transformed, and averaged to produce the spectrum estimate. Spectral power was integrated over three defined frequency bandwidths: "low" frequencies between 0.05 and 0.15 Hz; "high" (or respiratory) frequencies between 0.20 and 0.30 Hz; and all frequencies (i.e., "total power") below 0.50 Hz (23).

Motion Sickness Scoring: Symptoms were scored for each parabola using Graybiel et al.'s standard 16-point motion sickness scale (Graybiel, Wood, Miller, & Cramer, 1968). Incremental point values are assigned to different levels of severity of five major symptoms (nausea syndrome, skin color, salivation, drowsiness and sweating), and a single point is assigned to additional qualifying symptoms such as headache and dizziness. Symptoms were scored for each parabola and the maximum score achieved was used for subsequent statistical analyses.

Statistical Analyses

Student's t-test was used to examine gender differences in motion sickness severity, salivary amylase and total protein, high frequency R-R (HF_{R-R}) intervals, and a sympathovagal index (LF_{SBP}/HF_{R-R}). Forward stepwise multiple regression analysis was planned to determine the best potential predictors of motion sickness severity. However, the motion sickness data showed a bimodal distribution making regression analysis inappropriate. There was a natural break in the motion sickness scores

(≤ 8 points and ≥ 16 points) such that 10 subjects had 8 or fewer symptom points (none-mild sickness) and 6 subjects had 16 or more symptom points (moderate-severe sickness). Therefore, discriminant analysis was performed to determine the best combination of variables for correctly classifying individuals into two sickness severity groups (Duarte Silva & Stam, 1998).

Discriminant analysis is a multivariate statistical technique that allows one to determine a linear combination of dependent variables that best discriminate between two or more groups of subjects. Wilks' lambda is the statistic (equivalent to the F-test in analysis of variance) used to determine the statistical significance of the discriminatory power of the model. The value of Wilks' lambda ranges from 0 to 1, where 1 is no discriminatory power and 0 is perfect discriminatory power. The linear combination of a set of variables is called a discriminant function. The partial Wilks' lambda represents the unique contribution of a given variable to discriminate between groups (the lower the value, the greater its' discriminatory power). The canonical correlation squared is the proportion of variance in the discriminant function explained by the groups. All analyses were performed using Statistica (StatSoft, Inc., Tulsa, OK).

RESULTS

Table 1 provides the average maximum motion sickness scores, resting (pre-parabolic flight) levels of salivary amylase, HF_{R-R} , and SVI for the whole group and the two sickness severity groups of subjects (none-mild and moderate-severe). Ten of the subjects were males and 6 were females. Six of the 16 subjects (3 males and 3 females) vomited during parabolic flight. Student's t-tests for independent samples were performed to examine gender differences in symptom severity, resting

levels of salivary amylase, HF_{R-R} , and SVI. There were no significant differences between males and females for any of the variables tested.

Insert Table 1 about here

Because of the small n in this study we limited the number of variables used to classify subjects to three. Total protein was not included in the analysis. Total protein was significantly correlated with amylase, $r = 0.52$, $p < 0.038$, suggesting it would probably not add much to the correct classification of subjects. In addition, outliers (particularly in small n data sets) can significantly bias the analysis and lead to erroneous findings and interpretations. Therefore, the data for all the variables that were entered into the discriminant analysis were examined for the presence of outliers. No outliers were found for salivary amylase, HF_{R-R} , or SVI.

The discriminant analysis yielded a significant Wilks' lambda coefficient of 0.36, $df_{3,12}$; $p = 0.006$ and a canonical correlation of 0.80. The analysis correctly classified 87% (14/16) of the subjects. One subject in each of the sickness groups was misclassified. Table 2 provides the classification functions for the two groups and Table 3 provides the discriminant analysis summary. All three of the variables in the model significantly contributed to the discriminant function (Table 3).

Insert Table 2 and 3 about here

DISCUSSION AND CONCLUSIONS

Individual differences in motion sickness susceptibility and in physiological responses to motion sickness stimulus conditions (and differences across conditions) make prediction extremely difficult. Many investigators have reported differences between susceptible and insusceptible subjects for a variety of physiological parameters, however, these observations have not been consistently observed across different conditions (Harm, 1990; Harm, 2002).

Some possible explanations for the equivocal nature of findings of previous studies include differences in the symptom severity endpoint for stopping the motion sickness provocation test and test duration. The parabolic flight protocol in the current study does not allow for stopping the flight when subjects reach a predefined symptom severity level. It should be noted that all of our subjects in the moderate-severe group vomited at least once during the flight, whereas none of the subjects in the none-mild sickness group vomited.

The subjects with moderate-severe sickness in this study exhibited higher resting salivary amylase, HF_{R-R} , and SVI values than those with none-mild sickness. Higher amylase and SVI in subjects with moderate-severe sickness suggests they have higher resting sympathetic activity than those who experienced none-mild sickness. These findings are consistent with those described earlier (Gordon et al., 1994; Gordon et al., 1992; Schlegel et al., 2001). In contrast to previous observations that individuals with higher resting HF_{R-R} had fewer symptoms during motion sickness provocation tests (Uijtdehaage et al., 1992; Uijtdehaage et al., 1993), our subjects who experienced none-mild sickness had somewhat lower resting HF_{R-R} levels than those who experienced moderate-severe sickness.

In the earlier studies the motion sickness test was a circularvection drum and exposure duration was limited to 16 min (Uijtdehaage et al., 1992; Uijtdehaage et al., 1993). The stimulus intensity and duration was considerably less than the parabolic flight protocol used in the present study. It may be that greater fluctuations in efferent cardiac-vagal nerve traffic before mild and/or short duration exposures to motion sickness stimulus conditions provides some protection against the early symptoms (mediated by the sympathetic nervous system), whereas it may contribute to susceptibility to vomiting (mediated by the parasympathetic system) during more intense, longer duration conditions. Thus the direction of the relationship between HF_{R-R} and symptom severity may depend on the motion sickness stimulus conditions.

In conclusion, the linear combination of resting salivary amylase, HF_{R-R} , and SVI correctly classified 87% of the subjects in this study. This suggests that this combination of variables may be useful in predicting motion sickness severity and may have greater predictive capability than individual variables alone. A degree of caution is necessary in interpreting these results primarily because of the small subject population. Future research is clearly needed with a much larger population and assessment of the predictive capabilities of salivary amylase, HF_{R-R} , and SVI for different motion sickness stimulus conditions and different exposure durations.

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Table 1. Group Characteristics

	Whole Group	None-Mild Sickness	Moderate – Severe Sickness
Age	32.25 ± 1.71	31.4 ± 2.03	33.67 ± 3.21
Maximum MSS	9.0 ± 2.39	2.1 ± 0.84	20.5 ± 1.18
Amylase X 10 ⁻³	162.6 ± 35.53	110.6 ± 25.49	249.2 ± 75.82
HF _{R-R} X 10 ³	2.8 ± 0.52	2.5 ± 0.57	3.3 ± 1.06
SVI	7.5 ± 2.13	6.3 ± 1.89	9.5 ± 4.94

Values are means ± SE. R-R interval spectral powers are in ms²/Hz, salivary amylase is in IU/L. SVI = sympathovagal index (LF_{SBP}/HF_{R-R}, where LF_{SBP} is in mmHg²/Hz for SBP spectral power); MSS = motion sickness score; *n* = 16 (whole group), 10 (none-mild sickness), and 6 (moderate-severe sickness).

Table 2. Discriminant Analysis Classification Functions

Variable	None-Mild Sickness	Moderate-Severe Sickness
Amylase	0.00004	0.0001
HF _{R-R}	3.2551	5.1629
SVI	0.6466	1.0274
Constant	-8.63116	-22.4839

These classification functions can be used a priori in future studies to predict group assignment. The following formula is used to compute classification scores for individual subjects and then for the group: $C_i = C_{i1}V_1 + C_{i2}V_2 \dots C_{ip}V_p + C_{io}$, where C_i = classification score for group I ; C_{ij} 's = classification coefficient (weight) for the j th variable for the i th group; and V = the observed value for the respective case or the j th variable.

Table 3. Discriminant Analysis Summary

Variable	Wilks' Lambda	Partial Lambda	p-Level
Amylase	.8303	.4380	.002
HF _{R-R}	.7233	.5027	.005
SVI	.6258	.5027	.012