Orthostatic Intolerance and Motion Sickness after Parabolic Flight

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ABSTRACT

Orthostatic intolerance is common in astronauts after prolonged space flight. However, the "push-pull effect" in military aviators suggests that brief exposures to transitions between hypo- and hypergravity are sufficient to induce untoward autonomic cardiovascular physiology in susceptible individuals. We therefore investigated orthostatic tolerance and autonomic cardiovascular function in 16 healthy test subjects before and after a seated 2-hr parabolic flight. At the same time, we also investigated relationships between parabolic flight-induced vomiting and changes in orthostatic and autonomic cardiovascular function. After parabolic flight, 8 of 16 subjects could not tolerate a 30-min upright tilt test, compared to 2 of 16 before flight. Whereas new intolerance in non-Vomiters resembled the clinical postural tachycardia syndrome (POTS), new intolerance in Vomiters was characterized by comparatively isolated upright hypocapnia and cerebral vasoconstriction. As a group, Vomiters also had evidence for increased postflight fluctuations in efferent vagal-cardiac nerve traffic occurring independently of any superimposed change in respiration. Results suggest that syndromes of orthostatic intolerance resembling those occurring after space flight can occur after a brief (i.e., 2-hr) parabolic flight.

Key Words: postural tachycardia syndrome (POTS), microgravity, hypergravity, vomiting, autonomic, space flight

ORTHOSTATIC INTOLERANCE is common in astronauts after prolonged exposure to microgravity (6, 14). However, the existence of the so-called "push-pull effect" in military aviators—i.e., the heightened risk, in many high-performance pilots, of G-induced loss of consciousness during an extreme +G flight-maneuver in the *z* direction ($+G_z$) if a $-G_z$ flight-maneuver has just been completed (1, 30)—suggests that untoward autonomic cardiovascular physiology can be generated very rapidly under the right gravitational conditions. This rapidity is potentially confirmed by our own observation that many individuals who have just experienced even lesser extremes of hypo- and hypergravity during brief parabolic flights also develop lightheadedness that can persist after landing. One of the principal goals of this study, therefore, was to take advantage of the relatively short duration of parabolic flights (compared to space flights) to investigate the possibility that exposure to acute gravitational transitions alone might be sufficient to induce untoward autonomic cardiovascular physiology and to reduce orthostatic tolerance in susceptible individuals after landing.

Motion sickness is another common condition affecting both returning astronauts (44) and individuals returning from parabolic flight (25). To our knowledge, however, a prospective investigation of changes in orthostatic tolerance in individuals recovering from motion sickness has never been performed. Recently, Buckey et al. (6) have described a form of post-space flight orthostatic intolerance in two returning astronauts, possibly related to motion sickness, that was not characterized by any clear hypotensive event. A second, related goal of this study, therefore, was to utilize the inevitable motion sickness generated in susceptible individuals during and after parabolic flights to

investigate relationships between motion sickness and concomitant changes, if any, in autonomic cardiovascular and orthostatic function.

Our specific hypotheses were that: *1*) autonomic cardiovascular dysfunction and orthostatic intolerance do indeed occur with an increased frequency after a standard 2-hr parabolic flight; but that *2*) the type and/or degree of autonomic cardiovascular dysfunction and orthostatic intolerance necessarily differs in individuals who have and who have not vomited as a result of parabolic flight.

MATERIALS AND METHODS

Subjects. Sixteen healthy test subjects (ten men and six non-pregnant women, mean age 32 years, range 22-45 years) participated in the study, which was approved by the Johnson Space Center Institutional Review Board. All subjects were free of cardiopulmonary, renal or other systemic disease, and each gave written, informed consent after passing an U.S. Air Force Class III physical examination. In addition, all subjects were nonsmokers who had normal blood pressure (BP), hemoglobin/hematocrit, creatinine, electrolytes, liver function tests and urinalyses (including drug screens). Caffeine, alcohol, heavy exercise, anti-motion sickness medications and all other medications were strictly prohibited beginning 24 hours prior to any testing, which was commenced in the morning hours after a low-fat breakfast.

Parabolic flights and motion sickness scores. While loosely restrained at the waist, subjects flew four sets of ten 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 and to look forward at a

computer monitor placed immediately in front of them. As verified by an accelerometer mounted inside the aircraft, single parabolas consisted of the following three phases, each lasting approximately 20-25 s: *1*) "pull-up" with increased G-load of up to +1.8 G_z; *2*) microgravity (approximately 0.01 G_z); and *3*) "pull-out" with increased G-load of up to +1.8G_z (see ref. 48). During the entire inflight and postflight periods, motion sickness scores were estimated and recorded for each subject at 5 min intervals using Graybiel's standard 16-point scale (16). These scores were reduced (for simplification) to the maximum spot score attained during the entire protocol and the maximum spot score attained during postflight tilt testing approximately 40-70 min after landing. For statistical analyses, the maximum spot score overall was also used to separate subjects into two principal groups: Vomiters (maximum spot Graybiel score $\geq$ 16) and non-Vomiters (maximum spot Graybiel score < 16).

Cardiovascular and cerebrovascular measurements. Cardiovascular data were collected during identical pre- and postflight sessions in the supine and tilted-upright positions in a hangar facility at Ellington Air Field, Pasadena, TX. The preflight session occurred 1-5 days prior to parabolic flight and the postflight session immediately after parabolic flight. Prior to testing, subjects were first instrumented with *1*) electrocardiographic leads and electrodes (including an electrode for impedance measurements of abdominal-muscle respiratory excursions, Physio-Control, Redmond, WA); *2*) impedance cardiographic leads and electrodes (BoMed, Irvine, CA); and *3*) a finger photoplethysmographic device (Finapres 2300, Ohmeda, Englewood, CO) for beat-to-beat estimates of BP. The continuous cardiovascular signals from these devices were digitally recorded and integrated by using a special software program (28, 48) that

automatically entrains beat-to-beat heart rate (HR), stroke volume (SV) and mean BP (MBP) to create a real-time pictorial representation for beat-to-beat cardiac output [(CO) = HR x SV)] and total peripheral resistance [(TPR) = MBP/CO]. Throughout supine and upright testing, end-tidal CO_2 was also measured via a nasal probe (Puritan-Bennett, Wilmington, MA) while a 2 MHz flat ultrasound probe (TRANSPECT, Medasonics, Mountain View, CA) was mounted over the right temporal bone to obtain transcranial Doppler (TCD) recordings of blood flow velocities through the right middle cerebral artery. The principal TCD indices derived for the present study were the middle cerebral artery mean flow velocity (MCA-MFV) and the estimated cerebral vascular resistance (CVR_{est}), which is the estimated MBP at the level of the circle of Willis divided by the MCA-MFV (14). In certain representative subjects, to allow for a very detailed characterization of pre- to postflight changes in cardiovascular function in the context of upright tilt, we simply plotted the continuous trends for the TCD parameters alongside of simultaneous continuous trends for MBP, HR, SV, TPR and end-tidal CO_2 (see Figs. 1-4). While some error may be associated with the use of impedance cardiography for measurements of beat-to-beat SV, finger photoplethysmography for measurements of beat-to-beat BP, and TCD for measurements of beat-to-beat MCA-MFV, the combined techniques are nonetheless considered reliable for studying changes in cardiovascular function during upright tilt (40).

Both pre- and postflight, the specific sequential activities of test subjects were as follows: *1*) ambulation to the testing area; *2*) instrumentation (as noted above); *3*) supine rest for 15 min; *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 analyses; *5*) supine carotid-cardiac baroreflex testing; *6*) supine Valsalva maneuver testing; *7*) 3-5 min of additional supine rest; and, finally *8*) upright tilt testing. The majority of these activities are described in greater detail below. On the aircraft itself, both immediately before and after flight, subjects also performed Valsalva tests in the seated position. These seated tests complemented our earlier investigation (in the same subjects) of seated responses to Valsalva maneuvers during the inflight period (48).

Tilt tests. After supine autonomic testing both pre- and postflight, subjects were secured and pitched acutely (within 10-12 s) into the 80-degree head-up position by using a standard clinical autonomic tilt table (Tri W-G, Valley City, ND). A right arm-extension attached to the table was used during tilt to maintain the Finapres finger cuff at the level of the heart. Once obtained, the 80-degree head-up position was sustained for 30 min or until presyncopal vital signs and/or symptoms ensued. During min 1-10 of the upright position both pre- and postflight, some subjects also performed controlled breathing at 0.25 Hz for a total of 5 min (e.g., see Fig. 2).

In addition to the continuous cardiovascular and cerebrovascular measurements noted above, manual recordings of systolic and diastolic BP (SBP and DBP, respectively) were also obtained on a minute-to-minute basis before, during and after tilt via a sphygmomanometer attached to the non-extended (left) arm. During tilt, these recordings were increased to every 30 s upon the onset of new symptoms, TCD changes, or a marked decrease in BP or HR. For analyses, the manual BP recordings were averaged for each individual according to three epochs: epoch 1, the average of the two minute-to-minute BP recordings in the supine position immediately preceding upright tilt; epoch 2, the average of all BP recordings from minutes 1-10 of upright tilt or portion thereof

(excluding any data collected during controlled breathing or during the minute immediately prior to orthostatic failure, if failure occurred during this epoch); and, epoch 3, the average of one or more BP recordings from the last minute of upright tilt. The epochal averages for SBP, DBP and MBP from individual subjects were then used to derive corresponding averages for groups of subjects (i.e., whole group, Vomiters, non-Vomiters). A similar procedure was also performed for pulse pressure [(PP) = SBP-DBP], HR, SV, CO, TPR (derived from the manual measurements of MBP), end-tidal CO_2 and the TCD parameters. In one subject, the preflight TCD signal was corrupted such that it was not possible to calculate averages for MCA-MFV and CVR_{est} over any given epoch. In another subject, the averages for MCA-MFV and CVR_{est} during epoch 1 had to be obtained from a slightly earlier period in the supine position both pre- and postflight because of intermittent electrical interference in the preflight TCD signal.

Derivation of power spectra. Spectral powers for the supine position were derived from the 5-min series of consecutive R-R intervals, SBPs and DBPs collected during metronome-controlled breathing (5) at 0.25 Hz both pre- and postflight. 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 all subsequent pre- and postflight tests involving controlled frequency breathing. During data collection itself, based upon our observation of end-tidal CO_2 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.

For spectral analyses, the Welch algorithm for averaging periodograms (54) was used in accordance with the method of Rabiner et al. (42). 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 (24). We also calculated a "sympathovagal index", defined as the ratio of the low frequency power of SBP to the high frequency power of R-R intervals. This index resembles (but is not identical to) the sympathovagal index recently proposed by Novak et al. (39).

Carotid-cardiac baroreflex responsiveness. Both pre- and postflight, supine carotid-cardiac baroreflex responsiveness was measured in subjects via pressure changes applied to a tightly-sealing silastic neck chamber connected to a computer-controlled bellows (E-2000 Neck Baro Reflex System, Engineering Development Laboratories, Newport News, VA) (52). During held expiration, neck chamber pressure was raised to +40 mmHg, reduced to -60 mmHg, again raised to +40 mmHg, and then released, all in consecutive R-wave-triggered steps of $\pm$20 mmHg. This sequence was then repeated seven times and the responses averaged for each test subject. R-R interval responses to carotid baroreceptor stimulation, defined as carotid distending pressure (SBP minus neck pressure), were reduced to the maximum slope of the stimulus-response relation, the maximum range of R-R interval responses, and the operational point (11, 12). Maximum

slopes were identified with linear regression analyses applied to each set of three consecutive data pairs on the stimulus-response relation. Operational point, a measure of the amount of buffering capacity below baseline systolic pressure, was calculated as: [(R-R interval at 0 mmHg neck pressure minus minimum R-R interval)/R-R interval range] X 100%.

Although past studies of the carotid-cardiac baroreflex have concentrated on the response to a hypotensive stimulus train (+40 mmHg to –60 mmHg), we also measured the response to a hypertensive stimulus train (-60 mmHg to +40 mmHg) to explore the hysteresis of the system.

Valsalva measurements. Valsalva maneuvers were completed at an expiratory pressure of 30 mmHg for 15 s as previously described (48). Prior to the strains, which were performed in triplicate, subjects first had at least 15 min of rest in the assigned postural configuration (i.e., supine or seated). Each strain was also preceded and followed by at least 1 min of controlled frequency breathing at 0.25 Hz. To produce the strains, subjects blew into a mouthpiece connected by short plastic tube to a calibrated pressure gauge while the electrocardiogram, impedance cardiogram, and arterial and expiratory pressures were continuously recorded.

Because responses during phases I and III of Valsalva maneuvers are believed to reflect mostly mechanical changes (3, 46), we focused our analyses on variations in MBP during the "autonomic" Valsalva phases II and IV. Changes in MBP during phases II and IV were specifically calculated as follows: *1)* Δ early-phase II (phase II_e) was the change in MBP occurring between the maximal MBP value during phase I and the minimal MBP

value during phase II_e; *2)* Δ late-phase II (phase II_l) was the change in MBP occurring between the minimal MBP value during phase II_e and the maximal MBP value during phase II_l; and *3)* Δ phase IV was the change in MBP occurring between the minimal MBP value during phase III and the maximal MBP value during phase IV. In addition to the absolute changes in MBP, we also calculated the temporal duration of changes in the MBP response during Valsalva phases II_e and II_l (see ref. 48). During the immediate postflight period in the aircraft, one subject was not able to perform seated Valsalva maneuvers because of severe motion sickness.

Statistics. All results are reported as means ± SE with the exception of the Valsalva-related results, which are reported as means ± SD to facilitate comparison with our previously-published Valsalva-related results from the inflight period (48). Because normality was often violated, we used non-parametric statistics for all comparisons. Specifically, we used the Wilcoxon signed-rank test for within-group comparisons (i.e., before vs. after parabolic flight) and the Mann-Whitney rank sum test for between-group comparisons (i.e., Vomiters vs. non-Vomiters) (15). For all statistical determinations, significance was accepted at $P < 0.05$.

RESULTS

Overall responses to upright tilt. Nearly all subjects had cardiovascular changes postflight that were indicative of decreased orthostatic tolerance. Table 1, for example, shows pre- to postflight changes in supine and upright cardiovascular data for the entire group. In the supine position postflight compared to preflight, the group as a whole had

decreased DBP, MBP and TPR and increased SV and CO. During min 1-10 of the upright position (or portion thereof) postflight compared to preflight, the group as a whole had decreased SBP, TPR and MCA-MFV and increased CO. Finally, during the last minute of upright tilt postflight compared to preflight, the group as a whole had decreased DBP, MBP, TPR, MCA-MFV and end-tidal CO_2 and increased HR and CO. The decreased end-tidal CO_2 during the last minute of upright tilt postflight was not related to any change in the natural respiratory rate (i.e., 3.7 ± 0.2 breaths/min postflight vs. 3.7 ± 0.2 breaths/min preflight; $P > 0.05$).

Individual subject characteristics. Table 2 outlines the susceptibility of individual subjects to both motion sickness and orthostatic intolerance. Six of the 16 subjects vomited as a result of parabolic flight (shaded background) whereas ten did not. In addition, eight subjects—five of the six Vomiters and three of the ten non-Vomiters—had frank orthostatic intolerance postflight, defined as an inability to complete the 30-min postflight upright tilt test without limiting signs or symptoms. Two of the female Vomiters, however (subjects #15 and #16), were also the only subjects who had frank orthostatic intolerance preflight. In these two subjects, the specific mode of orthostatic failure was typical vasovagal presyncope (33) both pre- and postflight. The varying modes of orthostatic failure noted in the six subjects who were frankly intolerant only to postflight upright tilt are outlined as case studies below.

Tilt-related case studies:

A. Intolerant non-Vomiters. Although all ten non-Vomiters were tolerant to upright tilt before flight, three had frank orthostatic intolerance after flight. Importantly, all three of these subjects had scores of zero on the Graybiel motion sickness scale

throughout postflight cardiovascular testing, with two of the three being completely resistant to motion sickness at all times (Table 2). Figure 1 shows the continuous preflight (light tracing) and postflight (dark tracing) responses to upright tilt of one of these three subjects (#7, Table 2). Postflight, one of the most remarkable changes was the subject's postural tachycardia, which developed in conjunction with several other signs and symptoms (see the Fig. 1 legend). A second non-Vomiter who developed frank orthostatic intolerance postflight (subject #4, Table 2) had similar pre- to postflight changes in overall upright physiology. The principal difference was that subject #4 also had intermittent episodes of upright hypotension. Postflight, the responses to upright tilt of both subject #7 and subject #4 fulfilled diagnostic criteria for the clinical postural tachycardia syndrome (POTS) (27, 38, 39, 47, 49, 50).

Figure 2 shows corresponding pre- and postflight data from the final non-Vomiter who was intolerant to tilt only after flight (subject #5, Table 2). Although this subject also had POTS-like physiology postflight, she was distinguished from subjects #4 and #7 by having *1*) more instantaneous cardioacceleration, hypocapnia and cerebral vasoconstriction (relative to preflight) at the onset of her postflight upright tilt; *2*) more abrupt cardiovascular and cerebrovascular changes (specifically, a vasovagal-like episode) (17, 33) at the termination of her postflight upright tilt; and *3*) a greater difference between postflight SV and preflight SV throughout the upright period. This subject was also distinguished from the two Vomiters who had vasovagal episodes both pre- and postflight in that her postflight presyncope was heralded by a much more significant postural tachycardia relative to preflight.

B. Intolerant Vomiters. Three of the four Vomiters who were tolerant to upright tilt before flight developed frank orthostatic intolerance after flight (subjects #12, #13 and #14, Table 2). However, none of these individuals had absolute hypotension (SBP < 90) at the end of postflight upright tilt. Instead, all three had other signs and/or symptoms that warranted early tilt-test termination. Figure 3 shows an expanded portion of strictly postflight upright tilt data from one of these subjects (#13, Table 2). Shortly after landing, this subject's severe in-flight motion sickness had essentially resolved such that she was asymptomatic for the first 11 min of postflight upright tilt. However, near postflight upright min 11, the subject redeveloped mild nausea which progressed (without much warning) to frank retching and vomiting at postflight upright min 12.5. Of particular interest were the decrease in end-tidal CO_2, decrease in MCA-MFV and increase in CVR_{est} that developed concomitantly with the subject's prodromal nausea (not vomiting) at minutes 11-12.5 of the postflight tilt test. Consistent with the abrupt cerebral vasoconstriction, the subject also suffered from moderate lightheadedness at the time of her upright nausea. Of the other two Vomiters who completed uneventful preflight (but not postflight) tilt tests, one (subject #14, Table 2) had a postflight pattern very similar to that of subject #13 whereas the other (subject #12, Table 2) did not develop postflight upright nausea. Instead, subject #12 developed isolated (and limiting) lightheadedness after only 4 min of postflight upright tilt along with abrupt changes in end-tidal CO_2, MCA-MFV and CVR_{est} resembling those shown in Fig. 3. Because we know of no existing nomenclature for these nonhypotensive forms of orthostatic intolerance occurring in motion sick subjects, we have termed them "prostration intolerance" for the purposes of this paper.

Tolerant vs. intolerant subjects. As partially evidenced by data from the entire group (Table 1), postflight deficits in orthostatic tolerance such as exaggerated upright cardioacceleration and hypocapnia also occurred in so-called "tolerant" subjects. A specific case study is illustrated in Figure 4.

Tilt-related factors postflight that clearly distinguished tolerant subjects from frankly intolerant subjects are shown in Figure 5. Postflight, compared to the eight tolerant subjects, the eight frankly intolerant subjects had: *1*) decreased TPR in the supine position; *2*) decreased rather than increased TPR during the transition from the early portion of upright tilt (i.e., min 1-10 or portion thereof) to the end of upright tilt; and *3*) decreased TPR, SBP, and PP at the end of upright tilt.

Spectral power of supine R-R intervals and arterial pressures. Pre- to postflight changes in supine R-R interval and arterial pressure spectral powers for the entire group and for Vomiters vs. non-Vomiters are shown in Table 3. For the group as a whole, none of the R-R interval spectral parameters changed significantly from pre- to post-parabolic flight, nor did the sympathovagal index. However, the total power of arterial pressures increased in the group as a whole after flight (SBP, $P < 0.05$; DBP, $P < 0.01$).

After parabolic flight, the high frequency and total power of R-R intervals increased in Vomiters ($P < 0.05$ for total power only) but decreased (non-significantly) in non-Vomiters, leading to significant between-groups differences in these parameters. In addition, Vomiters had no changes in their arterial pressure spectral powers postflight whereas non-Vomiters, like the group as a whole, had increases in the total power of both SBP ($P < 0.05$) and DBP ($P < 0.01$). The non-significant decrease in the low frequency

power of SBP in Vomiters, and the non-significant increase in non-Vomiters, translated into a significant between-groups difference in this parameter postflight ($P < 0.05$). Sympathovagal index followed the same general pattern, with the difference between Vomiters and non-Vomiters reaching a similar level of significance postflight ($P < 0.05$).

The power spectral results might be summarized as follows: the Vomiter group tended to respond to parabolic flight with enhanced R-R interval variability whereas the non-Vomiter group tended to respond to parabolic flight with enhanced arterial pressure variability, primarily in the low frequency region.

Carotid-cardiac baroreflex responses. For the group as a whole, parabolic flight did not affect the maximum slope, range or operational point of the carotid-cardiac baroreflex. This was true for both the hypo- and hypertensive stimulus trains. However, postflight compared to preflight, during the hypotensive stimulus train, Vomiters had a significant increase in maximum slope (3.7 ± 0.6 vs. 2.4 ± 0.7 ms/mmHg, $P = 0.03$), a nearly significant increase in range (204 ± 31 vs. 153 ± 40 ms, $P = 0.06$), and no change in operational percent whereas non-Vomiters had no changes in any of these parameters.

Valsalva responses. Table 4 shows the pre- and postflight Valsalva responses of the whole group and of Vomiters vs. non-Vomiters. Postflight, in the seated (but not in the supine) position, the absolute MBP responses of the whole group and of Vomiters became significantly attenuated during Valsalva phases II_e and II_l ($P < 0.05$), whereas the absolute MBP responses of non-Vomiters were unchanged. In addition, the temporal duration of seated Valsalva phase II_e increased postflight in Vomiters ($P < 0.05$) but

decreased (non-significantly) in non-Vomiters, leading to a significant postflight between-groups difference in this parameter ($P = 0.02$).

Tolerant vs. intolerant non-Vomiters. Finally, because autonomic cardiovasular function was independently influenced by the presence of recent vomiting (Tables 3-4 and the baroreflex results above), we also analyzed postflight differences in supine autonomic cardiovascular function between non-Vomiters who were tolerant vs. frankly intolerant to postflight upright tilt (Figure 6). Compared to the seven non-Vomiters who were tolerant to postflight upright tilt, the three non-Vomiters who who were frankly intolerant had: *1*) greater percentage increases in the low frequency power of SBP and DBP from pre- to postflight ($P < 0.05$ for each); *2*) greater percentage increases in the sympathovagal index from pre- to postflight ($P < 0.05$); *3*) greater percentage increases in the absolute MBP response during supine Valsalva phase II_1 from pre- to postflight ($P < 0.05$); and *4*) a trend toward decreases (rather than increases) in the range ($P = 0.07$) and maximum slope ($P = 0.07$) of the hypotensive carotid-cardiac baroreflex from pre-to-postflight.

DISCUSSION

Our results indicate that exposures to short, repetitive gravitational transitions alone are sufficient to reduce orthostatic tolerance in susceptible individuals. This conclusion is supported not only by the fourfold increase in the number of subjects who developed frank orthostatic intolerance after (compared to before) parabolic flight, but also by the subtle postflight deficits in orthostatic tolerance that occurred in nearly all

individuals (Table 1, Fig. 4). Our data also indicate that subjects who have and who have not vomited as a result of parabolic flight develop differing syndromes of orthostatic intolerance as well as differing directional changes in autonomic cardiovascular function after flight. These differences are discussed in detail below.

Postflight reductions in orthostatic tolerance. After parabolic flight, frank orthostatic intolerance that was not present before flight took one of two general forms (Table 2): POTS-like intolerance (e.g., Figs. 1-2) and prostration intolerance (e.g., Fig. 3). POTS-like intolerance occurred only in non-Vomiters, whereas prostration intolerance occurred only in Vomiters. In the upright position postflight compared to preflight, both of these general forms of intolerance were characterized by relative hypocapnia and cerebral vasoconstriction. However, whereas notable postural tachycardia and either absolute hypertension or hypotension characterized POTS-like intolerance, these events did not typically characterize prostration intolerance.

POTS-like intolerance. A failure of the upright TPR response characterized POTS-like intolerance in this study (Figs. 1-2) and also characterizes the orthostatic intolerance of both returning astronauts (6, 14) and of patients with POTS who are prone to presyncope (47). Nonetheless, the occurrence of POTS-like intolerance after parabolic flight is surprising for at least two reasons. First, although clinical POTS is considered a model for abnormal cardiovascular function after space flight (27, 45, 50), parabolic flight does not involve prolonged exposures to microgravity, but only short, repetitive exposures to both micro- and hypergravity. Therefore, factors such as sustained cephalad fluid-shifting and disuse of baroreceptors cannot explain post-parabolic flight POTS. Other etiologies must be sought. Second, in the present study, all three of the individuals

who developed postflight POTS were resistant to motion sickness, with two of the three being completely resistant at all times (Table 2). Therefore, the postflight signs/symptoms of these subjects also cannot be explained on the basis of sickness-related factors such as nausea, fluid loss, etc.

One of the subjects who developed POTS after parabolic flight had upright hypertension rather than hypotension (Fig. 1). In the setting of clinical POTS, upright hypertension is especially suggestive of dysautonomia originating in the brainstem (27). Interestingly, signals from the otolith organs are known to modulate brainstem autonomic pathways involved in the control of the sympathetic nervous system (55, 56), and both astronauts and parabolic flyers receive novel inputs from these organs (i.e., prolonged otolith destimulation and repetitive otolith stimulation/destimulation, respectively). Therefore, it seems possible that altered otolith function could contribute to a transient central dysautonomia in susceptible individuals after either space flight or parabolic flight (55). Although both types of flight also undoubtedly directly influence other gravireceptors and baroreceptors, Colehour and Graybiel (7) have nonetheless demonstrated that unlike healthy subjects, individuals with bilateral labyrinthine deficiency do not have increases in their urinary excretion of norepinephrine immediately after an acrobatic flight stress. More recently, Jian et al. (21) have also demonstrated that cats with bilateral vestibular lesions can develop either orthostatic hypotension (i.e., in accord with the findings of others (9)) or, alternatively, orthostatic hypertension.

Prostration intolerance. The prostration form of orthostatic intolerance experienced by three of our motion sick subjects after parabolic flight might provide an explanation for the non-hypotensive form of orthostatic intolerance recently noted by

Buckey et al. (6) in two returning astronauts. Specifically, whereas end-tidal CO_2 and MCA-MFV were not measured in the astronaut study, in the present study, end-tidal CO_2 and MCA-MFV were always decreasing (and CVR_{est} was always increasing) in motion sick-susceptible subjects at the time of their most severe upright symptoms (e.g., Fig. 3). The fact that acute hypocapnia accompanied cerebral vasoconstriction in our upright motion sick subjects suggests that alterations in upright respiratory activity may be partially responsible for the lightheadedness of these individuals. The notion that acute hypocapnia alone is able to elicit lightheadedness, cerebral hypoperfusion and early presyncope in patients prone to orthostatic intolerance has recently been demonstrated conclusively by Novak et al. (40). However, in their patients, exaggerated hypocapnia during upright tilt was attributed to a compensatory respiratory response to inadequate peripheral vasoconstriction (40). On the other hand, in our motion sick subjects, the corresponding hypocapnia cannot reflect such compensation since it usually occurred before (or even outside of the context of) any overt failure of systemic vasoconstriction (e.g., Fig. 3). One possibility is that when nausea progresses during the development of motion sickness, it simply induces anxiety and therefore acute hyperventilation. However, inasmuch as motion sickness requires the presence of a functioning vestibular apparatus for induction (31), acute hyperventilation in motion sick subjects could also be driven by a change in supine-to-upright vestibulo-respiratory regulation (56) (i.e., by a brainstem-mediated as opposed to a cerebral hemisphere-mediated phenomenon). Yet another possibility (presently unproven) is that vestibulo-autonomic pathways—particularly those that travel via the cerebellum (29, 43)—might also have a more direct effect on cerebrovascular autoregulation in the context of motion sickness.

Hypocapnia and cerebral hypoperfusion. The changes in end-tidal CO_2 in our overall group postflight (Table 1) support another recent finding of Novak et al. (40); namely, that individuals who are prone to presyncope only develop significant hypocapnia (relative to healthy subjects) after assumption of the upright position. As in Novak et al.'s patients, exaggerated upright hypocapnia in this study (i.e., postflight) was also not due to any significant increase in the average upright respiratory rate. It may not necessarily follow, however, that exaggerated upright hypocapnia is therefore strictly attributable to a hyperventilation resulting from an increase in the average upright tidal volume (40). As an example, even though end-tidal CO_2 levels are often significantly decreased in healthy subjects after movement to the upright position (4, 41, 51), some investigators have noted concomitant increases in tidal volume and alveolar minute ventilation (41) whereas some have not (4, 23, 51). In addition, end-tidal CO_2 levels do not necessarily reflect arterial CO_2 levels in a consistent fashion across all postural conditions inasmuch as ventilation/perfusion mismatches and pulmonary dead space are relatively increased in the upright position (41).

Serrador et al. (51) have recently suggested that supine-to-upright decreases in end-tidal CO_2 in healthy subjects may reflect redistribution of blood and tissue CO_2 stores rather than changes in minute ventilation, alveolar ventilation, dead space, cardiac output or CO_2 production. If so, such redistribution could potentially explain some of the variable patterns of exaggerated upright hypocapnia that we noted postflight. Our subject #5, for example (Fig. 2), was unique in that she had a very early post- vs. preflight difference in upright end-tidal CO_2 that persisted in the face of grossly-equivalent controlled breathing from pre- to postflight (see especially the stippled area, Fig. 2).

Thus, at least during the early portions of postflight upright tilt, subject #5's relative hypocapnia was probably not due to hyperventilation, but rather to some other etiology, possibly CO_2 redistribution (51). On the other hand, like nearly all of the subjects who became presyncopal after flight, subject #5 also began to breathe more irregularly in the upright position as her overall condition worsened, presumably in an attempt to increase venous return and to activate other compensatory autonomic reflexes (40). Thus, hyperventilation probably contributed to the superimposed hypocapnia that began abruptly near min 22 of her postflight upright tilt test—i.e., just prior to her actual vasovagal event (Fig. 2). Rather than immediate upright hyperventilation, a greater initial venous redistribution of CO_2 in subject #5 might also be consistent with the exaggerated falls in central venous pressure that are known to occur at the onset of upright tilt in groups of healthy subjects who are ultimately prone to vasovagal presyncope (34).

Changes in autonomic cardiovascular function:

A. Vomiters. At least three findings from this study suggest that fluctuations in efferent vagal-cardiac nerve traffic are intrinsically heightened in the minutes after emesis. First, in the supine position postflight compared to preflight, Vomiters had increases in the total spectral power of R-R intervals (Table 3). This increase was not likely due to respiratory factors (5, 26) because, as described, we actively controlled respiration during the collection of these data. Second, Vomiters also had increases in the slope of the hypotensive carotid-cardiac baroreflex after flight, a change that is believed to reflect increased vagal control over the sinus node (11). This second finding might help explain why the carotid-cardiac baroreflex slope is not significantly decreased in an entire group of returning astronauts until 2-4 days after landing (11), when severe motion

sickness in some of the crewmembers is presumably no longer a factor. Third, immediately after flight in the seated position in the aircraft, Vomiters had temporally prolonged MBP responses during Valsalva phase II_e (Table 4). Temporal prolongation of phase II_e also occurs when seated Valsalva maneuvers are performed during parabolic microgravity (48)—i.e., when efferent cardiovagal influences on HR are presumably increased (35, 48).

The finding of increased R-R interval variability after emesis is not inconsistent with reports of decreased (10, 19) or unchanged (36) heart rate variability in previous human studies during the development of motion sickness because, in those studies, changes in heart rate variability were not studied in the context of actual vomiting. On the other hand, increased R-R interval variability after emesis is consistent with the increased "coefficient of variance of R-R intervals" observed in squirrel monkeys taken all the way to vomiting during a visual-vestibular stimulus (20). It may be, therefore, that the directional change in the variability of R-R intervals during motion sickness depends in part upon the degree of motion sickness attained, with prodromal symptoms (including moderate nausea) associated with decreased R-R interval variability (or with unchanged R-R interval variability when nausea-related respiratory alterations (2) are experimentally negated (36)) and the actual emetic and post-emetic periods associated with increased R-R interval variability. Taken together, these findings suggest that if a cardiac "stress response" independent of respiratory changes occurs during the development of motion sickness (19, 32) (it may not (36)), it is nonetheless superseded by increased fluctuations in vagal-cardiac nerve traffic during and/or after emesis itself, a situation that might be roughly paralleled during tilt testing when the acute development of vasovagal

presyncope is accompanied by increases in both the respiratory and non-respiratory fluctuations of R-R intervals (37).

B. Non-Vomiters. The relative increases in the low frequency power of SBP and DBP and in the sympathovagal index in non-Vomiters postflight (Table 3) were especially evident in the three non-Vomiters who developed frank orthostatic intolerance (Fig. 6). The supine autonomic changes in these three individuals were therefore again the most reminiscent of clinical POTS (39). However, unlike patients with clinical POTS, who have attenuated MBP responses during supine Valsalva phase II_l (47, 49, 50), the subjects with POTS-like intolerance in this study had, like astronauts returning from space flight (12), accentuated MBP responses during this same Valsalva phase (Fig. 6). Two factors might explain this apparent discrepancy. First, clinical POTS is a heterogenous disorder, and most patients with POTS do in fact have accentuated MBP responses during supine Valsalva phase II_l (P.A. Low, personal communication). Second, NASA investigators, including ourselves, typically calculate the magnitude of Valsalva phase II_l by using the delta MBP between the trough value in phase II_e and the peak value in phase II_l (12, 13, 48). On the other hand, until recently, most clinicians studying POTS have calculated the magnitude of phase II_l as the absolute or percent offset of the BP versus the baseline BP obtained prior to the beginning of the maneuver (27, 47, 49, 50). It should be noted that in situations where both phase II_e and phase II_l are determined to be accentuated by using the NASA method, the use of the earlier clinical method may determine that phase II_l is actually attenuated, depending upon the absolute increment in BP during phase I, the absolute decrement in BP during phase II_e, and the absolute increment in BP during phase II_l. Therefore, when cross-referencing the results of

studies employing the Valsalva maneuver, these differing historical methods of analyses should always be kept in mind.

Treatment perspectives. In the present study, the varying modes of orthostatic failure observed after parabolic flight suggest a slightly less severe version of the disparate modes of orthostatic failure recently described by Buckey et al. (6) in astronauts after space flight. The differences between the various modes of failure in both studies suggest that prophylaxis for orthostatic intolerance in returning crewmembers might best be individualized. Currently, NASA requires that all returning astronauts utilize two countermeasures against post-spaceflight orthostatic intolerance: G-suit inflation and oral fluid and salt loading. However, despite these in-flight countermeasures, up to 64% of crewmembers are still unable to complete a 10-min stand test after landing (6). Most crewmembers who still experience orthostatic intolerance after landing have postural tachycardia in conjunction with either a gradual (6) or immediate (14) failure of the TPR response and eventual orthostatic hypotension. Crewmembers who are especially prone to this syndrome might therefore benefit from additional late-inflight prophylaxis with a peripherally active pressor agent such as Midodrine (27). On the other hand, a non-centrally active medication like Midodrine might not be wholly efficacious in ameliorating the prostration intolerance of motion sick individuals, whose cardiovascular symptoms may be more strictly attributable to upright hyperventilation and cerebral vasoconstriction. In these individuals, additional late-inflight prophylaxis with a centrally-active antimotion sickness medication, plus or minus Midodrine, might be a more useful approach. Although orthostatic hypertension (as in one subject in the present study) has not been previously described in returning astronauts, yet other medications

might be useful in preventing/ameliorating that particular syndrome (27). Regardless of the specific type of intolerance, a crewmember who becomes lightheaded after landing might also be instructed to institute CO_2 rebreathing maneuvers (for example, closure of his or her launch/re-entry helmet visor if emesis is not imminent), since, if hypocapnia is present, such maneuvers will likely improve upright cerebrovascular function (40).

Limitations. An important limitation to this study was the absence of direct measurements of plasma volume. Although deficits in plasma volume correlate poorly with deficits in orthostatic tolerance in both returning astronauts (6, 14) and bed rested subjects (8), an equivalently poor correlation cannot be assumed to apply a priori to parabolic flyers. In addition, we did not measure levels of hormones such as catecholamines, arginine vasopressin (AVP), etc., which can be elevated after parabolic flight (25). In individuals who vomit as a result of such flight, AVP levels are especially elevated (i.e., up to 9-fold after landing) (25). Elevated AVP can in turn enhance arterial baroreflex sensitivity (i.e., in certain animal species) (18, 53) and, in humans, it can expand intravascular volume (22).

In summary, we studied orthostatic tolerance and autonomic cardiovascular function in 16 healthy test subjects before and after a seated 2-hr parabolic flight. After flight, eight of the 16 subjects could not tolerate a 30-min upright tilt test, compared to two of the 16 before flight. Of the six newly intolerant subjects, three had vomited as a result of parabolic flight (newly intolerant Vomiters) whereas three had not (newly intolerant non-Vomiters). After flight, the newly intolerant non-Vomiters (none of whom were significantly motion sick) developed a form of orthostatic intolerance resembling clinical POTS. This form of intolerance was characterized by an exaggerated

sympathovagal index in the supine position, an exaggerated hypocapnia and cerebral vasoconstriction in the upright position, postural tachycardia, a failure of the upright TPR response, and either absolute hypo- or hypertension. On the other hand, the newly intolerant Vomiters developed a form of orthostatic intolerance that was not characterized by a clear hypotensive or hypertensive event, but rather by comparatively isolated hypocapnia and cerebral vasoconstriction during lightheadedness and/or recurrent nausea in the upright position. During controlled breathing in the supine position postflight compared to preflight, Vomiters also had autonomic changes suggestive of increased fluctuations in efferent vagal-cardiac nerve traffic. The most important conclusion from this study is that syndromes of orthostatic intolerance resembling those occurring after space flight can occur after a brief (i.e., 2-hr) parabolic flight.

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FIGURE LEGENDS

Figure 1. Preflight (light tracing) and postflight (dark tracing) responses to upright tilt in a subject (#7, Table 2) who developed frank orthostatic intolerance during his postflight tilt test only. The lines within each tracing represent temporal regressions from the end of upright tilt back to the second minute of the upright position. CVR_{est}, estimated cerebral vascular resistance; MCA-MFV, mean flow velocity of blood in the right middle cerebral artery; CO_2, nasal end-tidal carbon dioxide level; MBP, mean blood pressure; HR, heart rate; SV, stroke volume; TPR, total peripheral resistance. Preflight, this subject completed the maximum 30-min of upright tilt in an unremarkable fashion. Postflight, however, he developed palpitations and severe lightheadedness, requesting premature termination of the tilt test near upright minute 21 (dark vertical line). His postflight signs included: *1*) progressive postural tachycardia; *2*) a gradual failure of the upright TPR response; *3*) mild relative hypertension; and *4*) relative hypocapnia and cerebral vasoconstriction with a reversal of the direction (compared to preflight) of the temporal regression slopes for CVR_{est}, MCA-MFV and CO_2. This subject did not experience notable motion sickness either during or after flight.

Figure 2. Preflight (light tracing) and postflight (dark tracing) responses to upright tilt in the lone subject (#5, Table 2) who had postural tachycardia as well as a vasovagal episode postflight but who completed an unremarkable tilt test preflight (see Fig. 1 for an explanation of abbreviations and temporal regression lines). The Finapres signal was unfortunately lost in this subject during postflight upright minutes 0-3.5. Nonetheless, her postflight vasovagal episode is clearly shown between the dark vertical lines (near

upright min 22.5), which represent the beginning and end, respectively, of emergent downward tilt. Note the abrupt decreases in MBP and HR (as well as the more abrupt decreases in TPR, end-tidal CO_2 and MCA-MFV, compared to Fig. 1) that occurred just prior to the emergent termination of this subject's postflight tilt test. During upright mins 5-10 both pre- and postflight (stippled area), this subject also performed metronome-controlled breathing at a frequency (0.25 Hz) that was slightly faster than her natural respiratory rate. The strong relationship between MCA-MFV and end-tidal CO_2 is illustrated by the similar de-trending (i.e., acute lowering) of these two parameters during controlled breathing both pre- and postflight.

Figure 3. Expanded view of min 8-14 only of the postflight response to the upright position in a subject (#13, Table 2) who experienced significant nausea and vomiting during parabolic flight (see Fig. 1 for an explanation of abbreviations). Although this subject was virtually free of motion sickness symptoms in the supine position 35-40 min after landing, she redeveloped nausea near upright min 11 of the postflight tilt test which rapidly progressed to frank retching and vomiting beginning at upright min 12.5. During this subject's mild nausea (open bar), prior to her actual emesis, she increased the depth of her abdominal respiratory-muscle excursions (bottom) and became relatively hypocapnic. At the same time, MCA-MFV decreased while CVR_{est} increased. During the subject's subsequent upright retching and emesis (shaded bar), exemplified by the inordinately large, paroxysmal abdominal respiratory-muscle excursions, a bradycardia developed in conjunction with a sharp, transient increase in SV. At the same time, end-tidal CO_2 and MCA-MFV decreased further while the Finapres-derived parameters

(MBP, TPR and CVR_{est}) swung wildly. Although there was no direct evidence for finger-cuff-related artifact during minutes 12.5-14 (the subject, leaning forward, used her non-cuffed hand to deposit her vomitus into a bag), we could not definitively exclude this possibility.

Figure 4. Preflight (light tracing) and postflight (dark tracing) responses to upright tilt in a subject (#3, Table 2) who was orthostatically tolerant both pre- and postflight as well as completely resistant to flight-induced motion sickness (see Fig. 1 for an explanation of abbreviations and temporal regression lines). The postflight changes experienced by this subject in the upright position (i.e., moderate postural tachycardia as well as mild hypocapnia and cerebral vasoconstriction relative to preflight) demonstrate that deficits in orthostatic tolerance also occurred in so-called "tolerant" subjects. In this individual, some of the changes noted postflight may have been related to his more frequent respiratory sighing (not shown).

Figure 5. Postflight tilt-related differences that separated subjects who were tolerant (n = 8) versus frankly intolerant (n = 8) to the upright position after flight. TPR, total peripheral resistance. *$P < 0.05$ versus tolerant subjects, Mann-Whitney rank sum test.

Figure 6. Postflight percent changes in measures of supine autonomic cardiovascular function in non-Vomiters who did and who did not develop frank intolerance to postflight upright tilt. n = 7 (tolerant non-Vomiters) and 3 (intolerant non-Vomiters), respectively. *$P < 0.05$ vs. tolerant non-Vomiters, Mann-Whitney rank sum test.

Table 1. *Whole group responses to upright tilt*

	SUPINE		MIN 1-10 UPRIGHT		LAST MIN UPRIGHT	
	Preflight	Postflight	Preflight	Postflight	Preflight	Postflight
SBP (mmHg)	116 ± 2	113 ± 3	113 ± 2	107 ± 3*	111 ± 3	106 ± 3
DBP (mmHg)	75 ± 2	72 ± 2*	80 ± 2	77 ± 2	81 ± 2	76 ± 2*
MBP (mmHg)	89 ± 2	85 ± 2*	91 ± 2	87 ± 2	91 ± 2	86 ± 2*
PP (mmHg)	42 ± 2	41 ± 3	32 ± 2	30 ± 3	30 ± 2	30 ± 3
HR (beats/min)	59 ± 2	61 ± 2	74 ± 3	79 ± 3	80 ± 4	86 ± 4*
SV (ml)	127 ± 8	131 ± 8*	81 ± 6	81 ± 4	75 ± 6	79 ± 7
CO (l/min)	7.4 ± 0.4	8.0 ± 0.5*	5.8 ± 0.3	6.3 ± 0.3*	5.8 ± 0.4	6.6 ± 0.5*
TPR (mmHg/l/min)	12.5 ± 0.8	11.3 ± 0.8*	16.3 ± 0.8	14.2 ± 0.6†	16.4 ± 1.0	13.7 ± 0.8*
MCA-MFV (cm/s)	63.5 ± 4.8	58.4 ± 4.3	56.1 ± 4.2	50.4 ± 4.0*	52.3 ± 4.2	46.8 ± 3.7*
CVR_{est} (mmHg/cm/s)	1.7 ± 0.2	1.8 ± 0.2	1.4 ± 0.1	1.8 ± 0.3	1.6 ± 0.2	2.0 ± 0.3
ET CO_2 (%)	4.6 ± 1.4	4.5 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.5 ± 0.2	4.0 ± 0.1†

Values are means ± SE. SBP, DBP, MBP and PP: systolic, diastolic, mean and pulse blood pressures, respectively; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MCA-MFV, middle cerebral artery mean flow velocity; CVR_{est}, estimated cerebrovascular resistance; ET CO_2, end-tidal carbon dioxide level. $n = 16$ except for MCA-MFV and CVR_{est}, where $n = 15$. Effect of parabolic flight (Wilcoxon signed-rank test): *$P < 0.05$ vs. preflight; † $P < 0.01$ vs. preflight.

Table 2. Motion sickness and orthostatic intolerance after parabolic flight

Subject # (Gender)	Max. M.S. score, overall, then → during postflight tilt	Weight loss postflight (Kg)	Frank orthostatic intolerance during postflight tilt?*
	Non-Vomiters		
1 (M)	0→ 0	0	no
2 (M)	0→ 0	0	no
3 (M)	0→ 0	0	no
4 (F)	0→ 0	0	POTS-like
5 (F)	0→ 0	0	POTS-like†
6 (F)	0→ 0	0	no
7 (M)	1→ 0	0	POTS-like
8 (M)	3→ 0	0	no
9 (M)	4→ 2	0	no
10 (M)	8→ 2	-1.0	No
	Vomiters		
11 (M)	**16+→ 0**	**0**	**no**
12 (M)	**16+→ 4**	**0**	**Prostration**
13 (F)	**16+→ 16+**	**-1.0**	**Prostration‡**
14 (M)	**16+→ 16+**	**-1.5**	**Prostration‡**
15 (F)	**16+→ 4**	**-1.5**	**Vasovagal§**
16 (F)	**16+→ 6**	**0**	**Vasovagal§**

Max. = maximum, M.S. = motion sickness, with score defined on the basis of Graybiel's 16-point scale (16). Unshaded background, non-Vomiters; shaded background, Vomiters. *See text for a discussion of the various types of frank postflight orthostatic intolerance. POTS = postural tachycardia syndrome. †Also had vasovagal features, see text. ‡Upright position during the postflight tilt test led to renewed nausea and vomiting and therefore to orthostatic intolerance. §Also had frank orthostatic intolerance preflight.

Table 3. *Spectral power of supine R-R intervals and arterial pressures pre- and postflight*

	Whole Group		*Vomiters (V)*		*Non-Vomiters (nV)*		*V vs. nV*	
	Preflight	Postflight	Preflight	Postflight	Preflight	Postflight	*Preflight*	*Postflight*
Spectral power of R-R intervals								
LFP_{R-R} x 10^3	1.96±0.25	2.93±0.48	1.91±0.41	3.39±0.57	1.99±0.35	2.65±0.69	NS	NS
HFP_{R-R} x 10^3	2.79±0.52	4.12±1.49	3.32±1.06	7.41±3.57	2.47±0.57	2.14±0.73	NS	‡
TP_{R-R} x 10^3	8.62±1.39	10.81±1.93	7.89±1.76	16.65±3.29*	9.06±2.02	7.31±1.64	NS	‡
Spectral power of systolic blood pressures								
LFP_{SBP}	11.70±1.96	17.19±2.71	12.37±3.21	9.68±2.78	11.30±2.61	21.69±3.33	NS	‡
HFP_{SBP}	4.93±0.81	3.51±0.56	5.29±1.26	4.76±1.28	4.71±1.10	2.76±0.34	NS	NS
TP_{SBP}	61.29±12.11	89.62±12.70*	66.22±28.7	67.63±13.26	58.33±10.67	102.81±17.89*	NS	NS
Spectral power of diastolic blood pressures								
LFP_{DBP}	5.97±0.78	8.67±1.45	6.03±0.93	5.63±1.41	5.99±1.06	10.02±1.95	NS	NS
HFP_{DBP}	0.92±0.19	1.67±0.80	1.41±0.39	3.21±1.93	0.76±0.18	0.75±0.12	NS	NS
TP_{DBP}	19.12±2.61	32.62±4.69†	19.52±2.82	24.41±5.09	19.52±3.69	35.19±6.61†	NS	NS
Sympathovagal index								
LFP_{SBP}/HFP_{R-R}	11.11±6.10	26.77±15.50	19.12±16.3	2.29±0.94	6.31±1.89	41.46±24.01	NS	‡

Values are means ± SE in (ms^2/Hz) for R-R interval spectral powers and means ± SE in ($mmHg^2$/Hz) for arterial pressure spectral powers. n = 16 (whole group), 6 (Vomiters) and 10 (non-Vomiters), respectively. LFP, low frequency power; HFP, high (or respiratory) frequency power; TP, total power; SBP, systolic blood pressure; DBP, diastolic blood pressure. Within-group changes (Wilcoxon signed-rank test): *$P < 0.05$ vs. preflight; †$P < 0.01$ vs. preflight. Between-group changes (Mann-Whitney rank sum test): ‡$P < 0.05$; NS, no significant differences noted.

Table 4. *Effect of parabolic flight on responses to Valsalva maneuvers*

	Whole Group		*Vomiters (V)*		*Non-Vomiters (nV)*		*V vs. nV*	
	Preflight	Postflight	Preflight	Postflight	Preflight	Postflight	*Preflight*	*Postflight*
Absolute change in MBP during Valsalva phases II_e, II_l and IV: Supine								
Δ phase II_e	-14.78± 7.88	-13.40± 7.21	-14.65± 5.76	-9.39± 3.13	-14.88± 9.22	-15.80± 8.00	NS	NS
Δ phase II_l	11.17± 5.66	13.25± 6.12	11.46± 5.98	12.71± 3.62	10.99± 5.79	13.59± 7.41	NS	NS
Δ phase IV	20.92±10.11	22.53± 7.25	20.02±10.19	18.92± 7.03	21.47±10.58	24.70± 6.79	NS	NS
Absolute change in MBP during Valsalva phases II_e, II_l and IV: Seated								
Δ phase II_e	-22.34± 9.99	-18.05± 9.88*	-23.33± 8.46	-15.96± 7.47*	-21.85±11.08	-19.10±11.11	NS	NS
Δ phase II_l	21.39±11.07	15.61± 9.63*	15.96± 7.96	10.20± 7.18*	24.11±11.74	18.32± 9.85	NS	NS
Δ phase IV	25.19±15.36	21.16±12.81	26.16±22.17	23.58±18.36	24.70±12.16	19.97±10.02	NS	NS
Temporal duration of intrastrain Valsalva phases II_e and II_l: Supine								
II_e duration	7.19±1.07	6.78±1.32	6.90±0.84	6.95±1.08	7.36±1.19	6.67±1.49	NS	NS
II_l duration	5.64±1.28	5.96+1.35	5.83±1.03	5.89±1.08	5.52±1.44	6.00±1.54	NS	NS
Temporal duration of intrastrain Valsalva phases II_e and II_l: Seated								
II_e duration	6.12±1.33	6.09±1.34	5.94±1.55	7.26±1.41*	6.21±1.28	5.50±0.89	NS	†
II_l duration	6.82±1.47	6.29±1.52	6.24±1.33	4.78±1.60	7.11±1.52	7.04±0.75	NS	NS

Values are means ± SD in mmHg for absolute changes in mean blood pressure (MBP) and means ± SD in s for temporal changes in phases II_e and II_l. n = 16 (whole group supine), 6 (Vomiters supine), 10 (non-Vomiters supine or seated), 15 (whole group seated), and 5 (Vomiters seated), respectively. Postflight, seated strains were performed in the aircraft 5 min after landing whereas supine strains were performed in the hangar 30-40 min after landing. Within-group changes (Wilcoxon signed-rank test): *$P < 0.05$ vs. preflight. Between-group changes (Mann-Whitney rank sum test): †$P = 0.02$; NS, no significant differences noted.

FIG 1

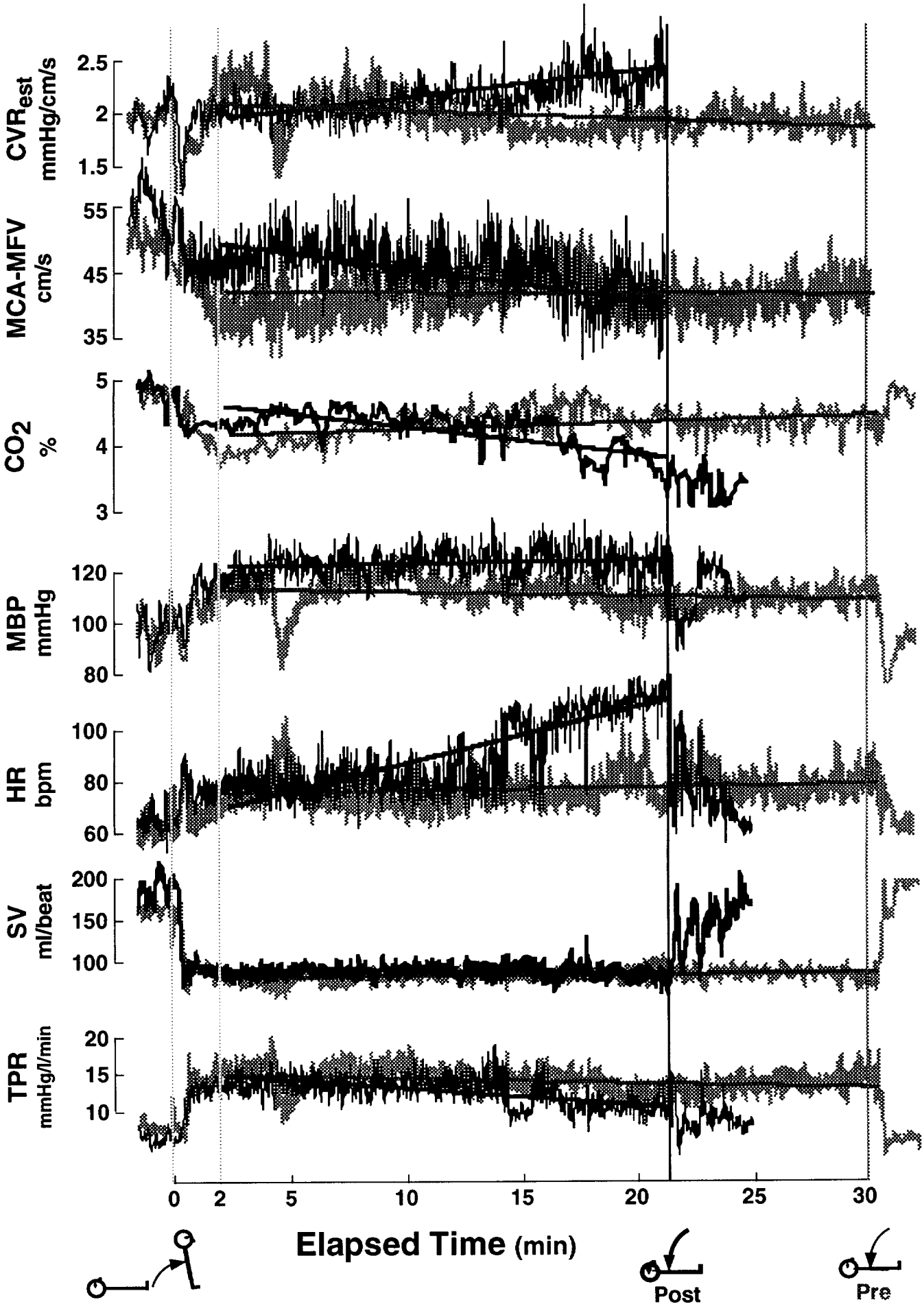

CVR$_{est}$ mmHg/cm/s
2.5
2
1.5
MCA-MFV cm/s
55
45
35
CO_2 %
5
4
3
MBP mmHg
120
100
80
HR bpm
100
80
60
SV ml/beat
200
150
100
TPR mmHg/l/min
20
15
10
0
2
5
10
15
20
25
30
Elapsed Time (min)
Post
Pre

FIG 2

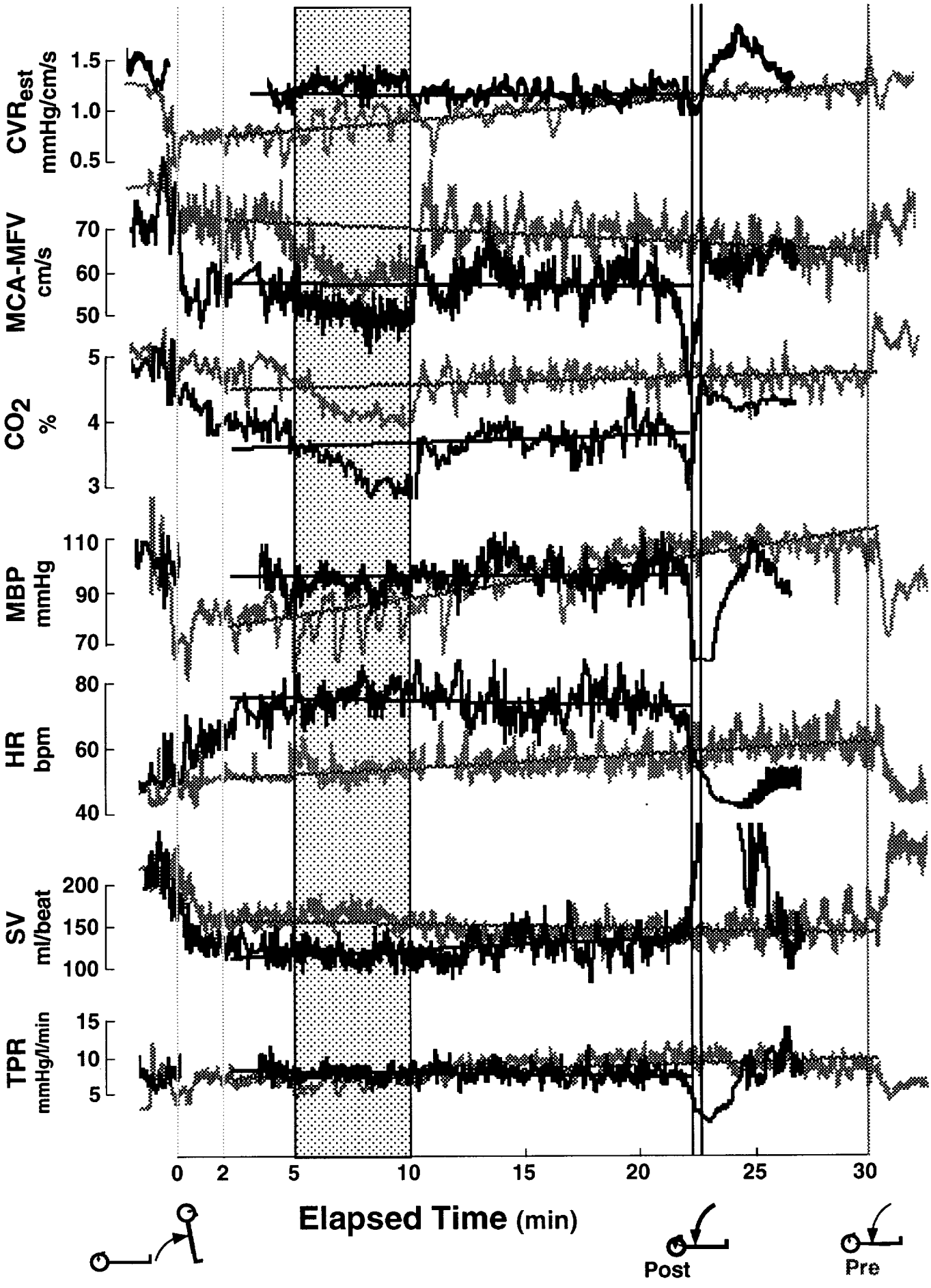

CVR$_{est}$ mmHg/cm/s
1.5
1.0
0.5
MCA-MFV cm/s
70
60
50
CO_2 %
5
4
3
MBP mmHg
110
90
70
HR bpm
80
60
40
SV ml/beat
200
150
100
TPR mmHg/l/min
15
10
5
0
2
5
10
15
20
25
30
Elapsed Time (min)
Post
Pre

FIG 3

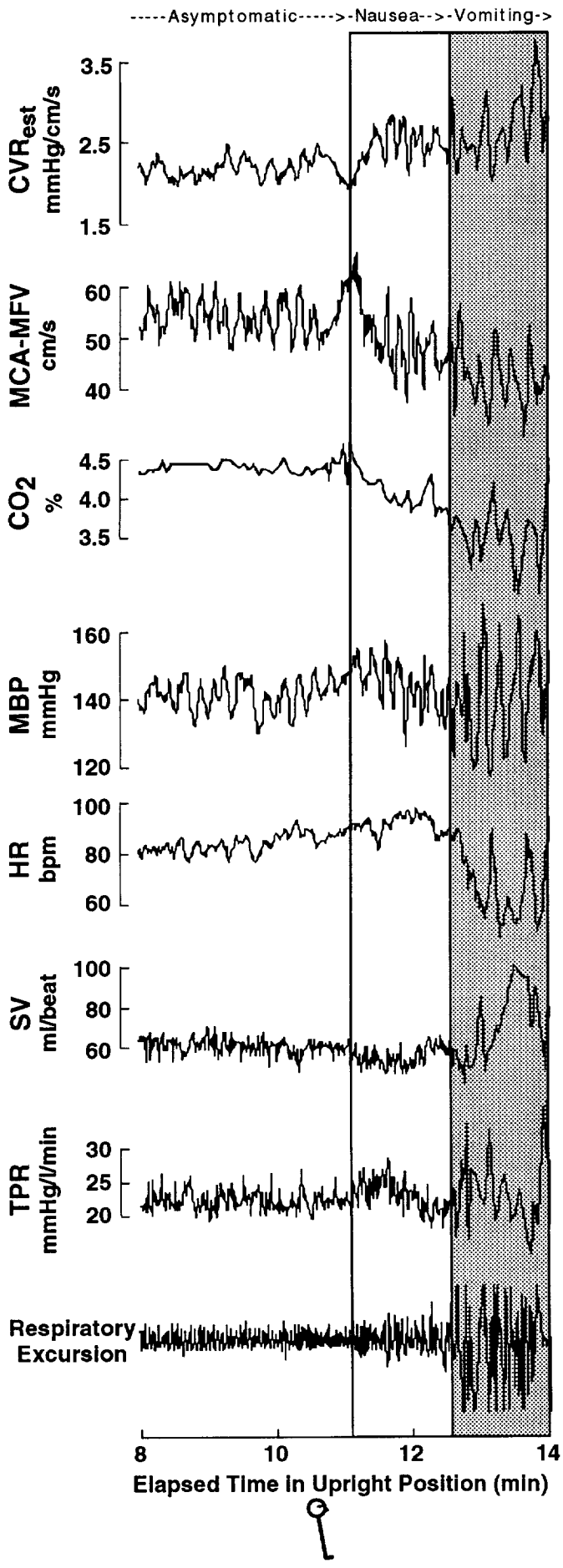

-----Asymptomatic----->-Nausea-->-Vomiting->
CVR$_{est}$ mmHg/cm/s
3.5
2.5
1.5
MCA-MFV cm/s
60
50
40
CO_2 %
4.5
4.0
3.5
MBP mmHg
160
140
120
HR bpm
100
80
60
SV ml/beat
100
80
60
TPR mmHg/l/min
30
25
20
Respiratory Excursion
8
10
12
14
Elapsed Time in Upright Position (min)

FIG. 4

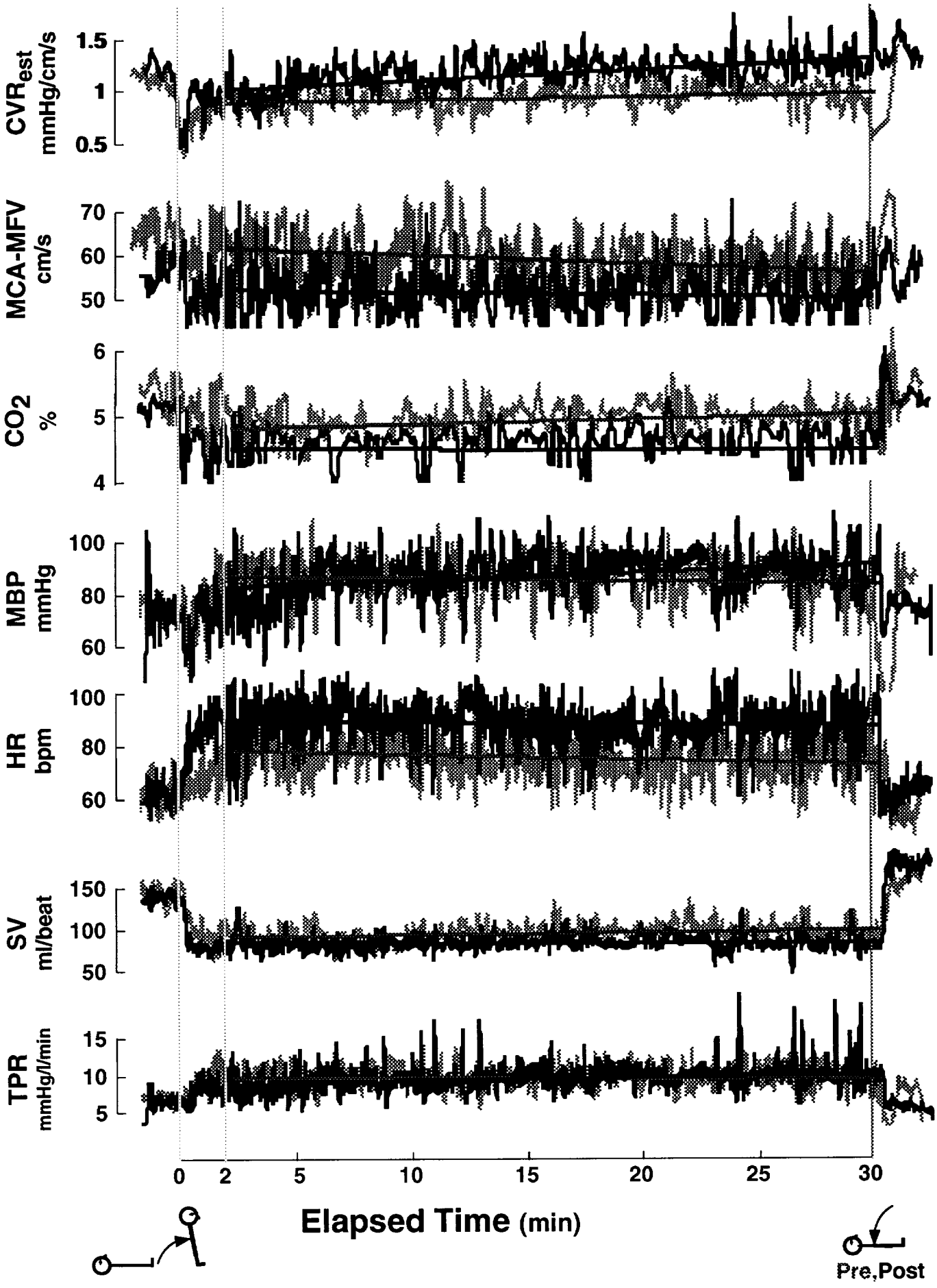

CVR est mmHg/cm/s
1.5
1
0.5
MCA-MFV cm/s
70
60
50
CO2 %
6
5
4
MBP mmHg
100
80
60
HR bpm
100
80
60
SV ml/beat
150
100
50
TPR mmHg/l/min
15
10
5
0
2
5
10
15
20
25
30
Elapsed Time (min)
Pre,Post

FIG. 5

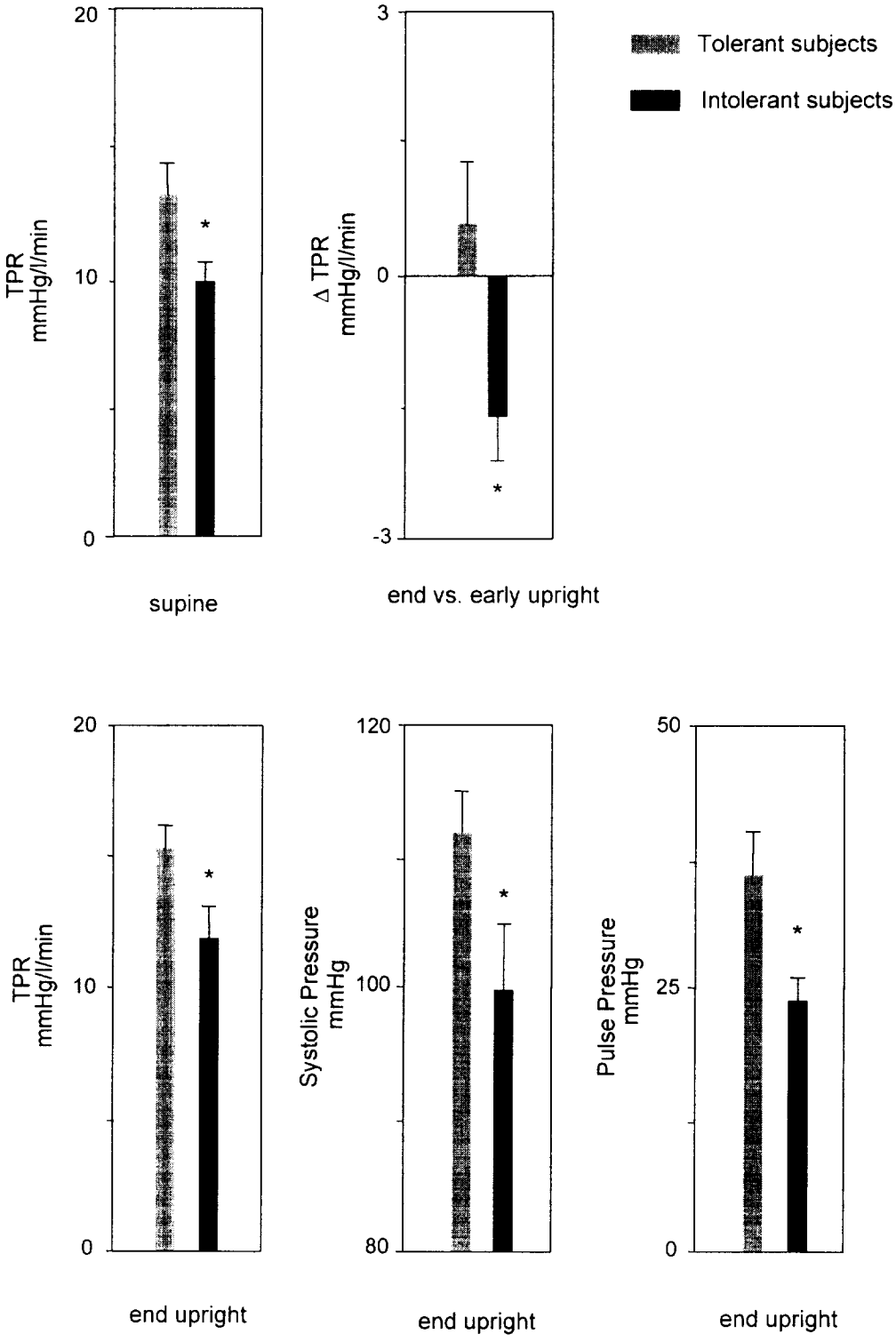
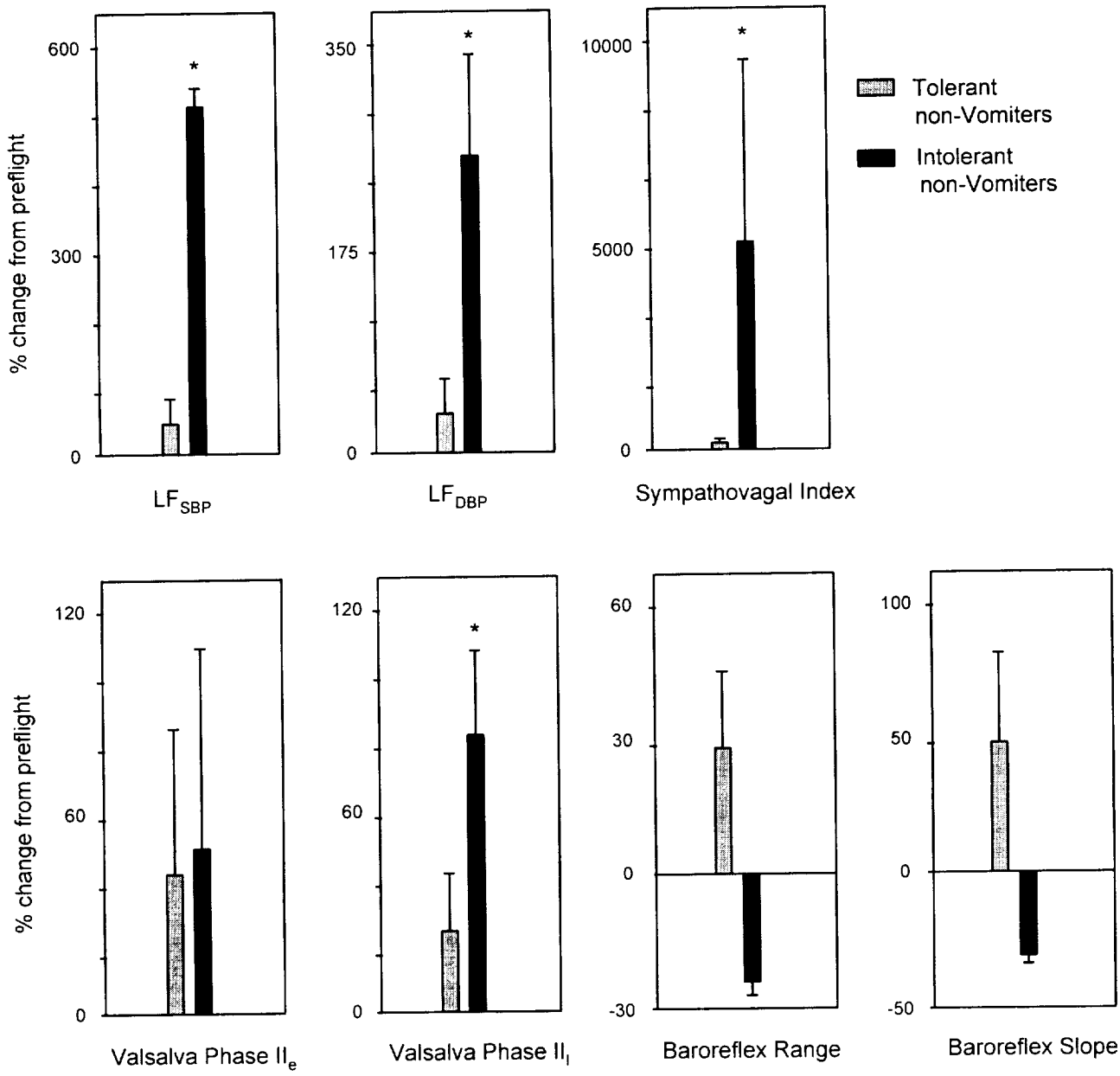

Tolerant subjects
Intolerant subjects
TPR
mmHg/l/min
20
10
0
*
supine
Δ TPR
mmHg/l/min
3
0
-3
*
end vs. early upright
TPR
mmHg/l/min
20
10
0
*
end upright
Systolic Pressure
mmHg
120
100
80
*
end upright
Pulse Pressure
mmHg
50
25
0
*
end upright

FIG 6


% change from preflight
600
300
0
*
LF SBP
350
175
0
*
LF DBP
10000
5000
0
*
Sympathovagal Index
Tolerant non-Vomiters
Intolerant non-Vomiters
% change from preflight
120
60
0
Valsalva Phase IIe
120
60
0
*
Valsalva Phase IIl
60
30
0
-30
Baroreflex Range
100
50
0
-50
Baroreflex Slope