Neuroendocrine and Immune Responses to 16-Day Bed Rest with Realistic Launch and Landing G Profiles

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Background: Spaceflight is associated with increased glucocorticoids and catecholamines, both well-known for their immunosuppressive effects. The objective of this study was to develop a model of spaceflight by using a human centrifuge to reproduce launch and landing G forces along with bed rest to simulate microgravity. ***Hypothesis:*** Acute changes in G forces are causal factors in neuroendocrine and immune changes. ***Methods:*** Ten subjects underwent realistic launch G-force profiles followed by 16 d of 6° head-down tilt bed rest. At the end of the bed rest, subjects were subjected to realistic landing G-force profiles. Stress hormones and changes in leukocyte and lymphocyte subsets were measured in blood and urine samples over the course of the study. ***Results:*** Similar to shorter Shuttle missions (i.e., ≤ 9 d), plasma cortisol was significantly decreased at simulated landing while urinary epinephrine was significantly increased. Urinary cortisol was significantly increased after simulated launch. The pattern of leukocyte and lymphocyte changes also mirrored the changes found in shorter 9-d spaceflights. ***Conclusions:*** These data suggest a role for both catecholamines and glucocorticoids in mediating changes in leukocyte and lymphocyte subsets during simulated microgravity coupled with hypergravity. Our results were also strikingly similar to those from actual Shuttle missions and support our conclusion that we have developed a model of spaceflight.

Keywords: Stress, microgravity, hypergravity, leukocyte trafficking.

CHANGES IN PERIPHERAL blood leukocytes and lymphocytes after spaceflight have been well documented (6,18,21,27,30,33). They include increased white blood cell (WBC) counts, increased neutrophils, and decreased eosinophils. Monocytes and lymphocyte subsets (e.g., CD4+ T cells) are either increased, decreased, or are unchanged depending on mission length. In particular, mission duration has a direct effect on the pattern and magnitude of stress hormone levels. Shorter Shuttle missions (i.e., < 9 d) are associated with greater 24-h urinary catecholamine levels postflight (22,31); this effect diminishes on longer missions (i.e., 16 d), at which time leukocyte and lymphocyte redistribution appears to be predominantly driven by the hypothalamic-pituitary-adrenal axis (31).

Notably, acute increases in cortisol have also been found on flight day 1 (15,29), presumably due in part to the stress of launch. During the Spacelab Life Science-1 mission, 24-h urinary cortisol levels returned to preflight levels after the first day of flight whereas on the Spacelab Life Science-2 mission they remained significantly elevated throughout most of the mission (15). The increased cortisol is biologically relevant in that increased neutrophils, in particular band neutrophils, were found just after launch on Spacelab-1 (16), which would be consistent with the spike in cortisol levels. Elevated glucocorticoids, known for their immunosuppressive effects, may also provide an explanation for the reduced delayed-type hypersensitivity response reported during Shuttle missions (32). Thus, the physical environment and psychological/physiological stressors associated with spaceflight may have a significant influence on leukocyte trafficking and function. These variables include confinement, isolation, sleep deprivation, noise and vibration, acceleration forces, and increased radiation. It will be important to determine the influence of various components of spaceflight (e.g., hypergravity, microgravity, psychological stress, radiation, etc.) to aid in the development of targeted countermeasures.

Current ground-based analogs that model certain aspects of spaceflight include, among others, Antarctic expeditions and head-down tilt bed rest. We have previously reported on immune and viral changes in the Australian Antarctic winter-overs (20,34). Similar to spaceflight studies, we found increased viral reactivation along with decreased cellular immunity. The microgravity portion of spaceflight is modeled by head-down tilt bed rest and has been used to study the cardiovascular, muscle, and bone systems (2,11,17). Our results

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indicated that the Australian Antarctic group was an acceptable ground-based model of psychological stress (isolation, confinement, etc.). However, the Antarctic model lacks important physiological changes associated with microgravity (i.e., bone and muscle loss). Bone and muscle loss are hallmark features of bed rest, but the acute changes in stress hormones that occur after Shuttle launch and landing are absent. Lack of a suitable ground-based model that simulates the multiple gravitational changes that occur during spaceflight (hypergravity at launch, microgravity during flight, hypergravity at landing) has limited investigations on how gravitational changes affect the neuroendocrine and immune systems.

We report here on the development of a model of shorter-duration spaceflight. To mimic the acceleration forces associated with launch and landing, subjects were spun in a human centrifuge using the same G-force profile that astronauts undergo during actual spaceflight. To mimic microgravity in between simulated launch and landing, subjects were put into 6° head-down tilt bed rest for 16 d. Stress hormone levels and leukocyte subsets from bed rest subjects were then compared to those obtained from 9-d and 16-d Shuttle missions.

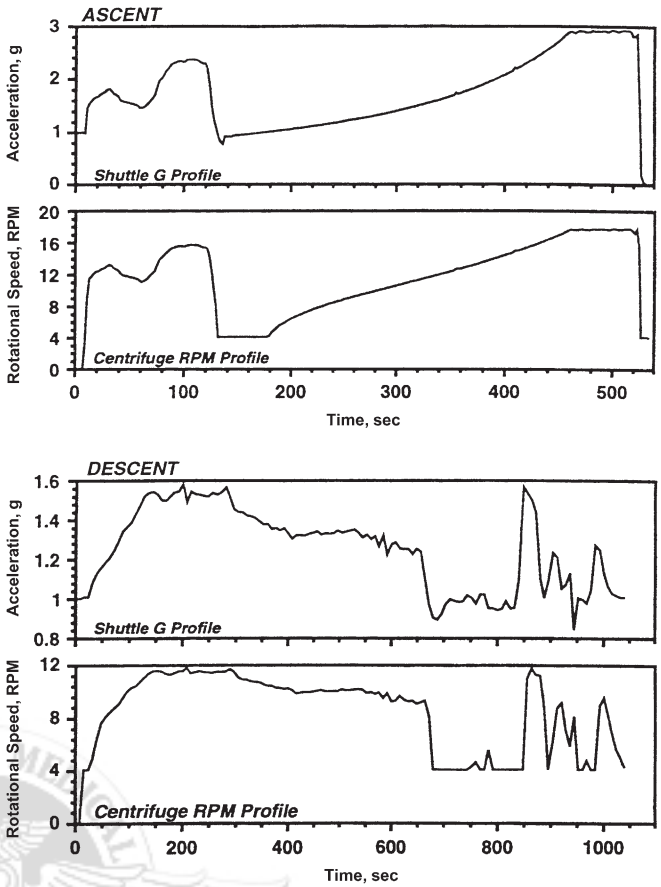

Fig. 1. Modeling of Shuttle G profiles (ascent and descent) by the Brooks centrifuge. (A–Upper) Launch profile from STS-56 liftoff: 1) SRB burnout; 2) SRB separation;, 3) "3 G throttle back"; and 4) main engine shutdown. (B–Lower) Landing profile of STS-56 touchdown: 5) energy burnoff; 6) approach maneuvers. The Shuttle G-force profiles were replicated by the rotational speeds shown.

METHODS

Subjects: A total of 10 subjects participated in this study (5 male and 5 female). Subjects were obtained from the Johnson Space Center (JSC) Test Subject Facility, and each one passed an Air Force Class III physical. The ages of the subjects ranged from 25–45 yr of age (mean 38 ± 2). This protocol was approved by the JSC and Brooks Air Force Base Institutional Review Boards, and informed consent was obtained from all participants.

Design: Peripheral blood (~8 a.m.) and 24-h urines were collected at simulated launch minus 10 d (L-10) and L-4 d; these collections took place at JSC. One day before simulated launch, subjects started 24-h urine collections and were transported to the Chronobiology and Sleep Laboratory (CASL) at Brooks Air Force Base for overnight stay. Starting the next morning, urine was collected continuously throughout the 16-d study. Subjects were fed a standard varied diet (approximately 55% carbohydrate, 30% fat, and 15% protein) on a typical three meals a day at the CASL. Blood samples were taken ~8 a.m., and the subjects were then transported to the centrifuge facility. Subjects were spun at the same G forces (G_x) and duration that astronauts undergo during launch (**Fig. 1A**) and then placed on a gurney and transported back to the CASL followed by 16 d of 6° head-down tilt bed rest (BR). Another blood sample was collected 4 h post "launch." Peripheral blood samples were also drawn on BR+4, BR+8, and BR+12. On day 16, blood samples were drawn at 8 a.m. and then the subjects were transported back to the centrifuge facility. The subjects then underwent centrifugation to mimic the Shuttle landing G-force (G_z) profile (**Fig. 1B**). Afterwards, the subjects were no longer confined to bed rest and allowed to move around freely with supervision. Four hours "post-landing" (R+0), peripheral blood samples were again taken. After a medical clearance examination the next morning, subjects were transported back to JSC on R+1. Blood and 24-h urine samples were again collected at R+3 and R+15.

Measurement of stress hormones: The measurement of hormones has been previously described (30). Urinary cortisol was measured by radioimmunoassay. Urinary catecholamines (epinephrine, norepinephrine) were measured by high-performance liquid chromatography. Plasma cortisol was measured using commercially available kits (Diagnostic Systems Laboratories, Webster, TX). Samples were batch analyzed to minimize interassay variation.

Leukocyte subset analysis: Absolute numbers of leukocytes per milliliter of blood, as well as the percentage of leukocyte subsets, were determined by a Coulter blood cell analyzer (Coulter Electronics, Hialeah, FL).

Immunofluorescent staining: Phenotypic analysis of whole blood was performed by flow cytometry as previously described (29). Fluorescent antibodies conjugated to various fluorochromes (obtained from Becton-Dickinson, Mountain View, CA) were added to whole blood (100 μl) and incubated at room temperature for

30 min. Red blood cells were lysed using FACSLyse (Becton-Dickinson). The cells were then washed once, resuspended in paraformaldehyde, and analyzed on a FACSCalibular flow cytometer (29). A minimum of 20,000 events was collected for each sample.

Statistical analysis: Statistical analysis was performed using SigmaStat 2.03 (Systat Software Inc., San Jose, CA). The Student's *t*-test was used for paired (intragroup) data. Data from multiple time points were analyzed by ANOVA followed by multiple-comparison procedures (Tukey's test). The percent change in each hormone for each subject was calculated as follows: ([R+0 level - L-10 level]/L-10 level) × 100. Results are expressed as means ± SE; $P < 0.05$ was considered significant.

RESULTS

We initially sought to compare stress hormone data (L-10 vs. R+0) from this model to our prior results from actual 9-d and 16-d spaceflights (31). A comparison of data is shown in **Fig. 2**. Similar to 9-d space missions, plasma cortisol was significantly decreased at R+0 in the bed rest subjects (27.0 ± 4.2 vs. 17.6 ± 1.5 ug · dl^{-1}) while it was increased in astronauts undergoing 16-d missions. For urinary cortisol, a nonsignificant increase occurred in the bed rest subjects (14.9 ± 3.6 vs. 32.1 ± 8.6 ug/24 h; $P = 0.08$). A nonsignificant increase was also observed after the 9-d missions, while a significant increase in urinary cortisol was found after the 16-d missions.

We then assessed changes in circulating leukocytes and lymphocytes as compared to 9- and 16-d Shuttle missions. As shown in **Table I**, white blood cells (WBCs) and neutrophils were significantly increased ($P < 0.05$) after the Shuttle landings and simulated landing. Lymphocytes were significantly increased after the 16-d bed rest ($P < 0.05$); a nonsignificant increase in lymphocytes were also found after 16-d spaceflights while no changes were found after the 9-d missions. Monocytes were significantly increased ($P < 0.05$) at simulated landing. A nonsignificant increase in monocytes was found after 9-d spaceflights whereas a significant decrease was found after 16-d spaceflights. Eosinophils were significantly decreased ($P < 0.05$) after the 9-d spaceflights and the 16-d bed rest. We then measured changes in CD3+CD4+ T-cells. As shown in Table I, significant increases were found after simulated landing in the BR subjects; significant increases were also found after the 9-d missions.

As multiple samples were taken throughout the study, a kinetic analysis of stress hormone changes was undertaken. As shown in **Fig. 3**, a significant spike in 24-h urinary cortisol was found at BR+1; cortisol remained elevated throughout bed rest as compared to pre-bed rest time points ($P = 0.02$). Urinary epinephrine on the other hand did not significantly increase after simulated launch. However, after simulated landing there was a significant increase in 24-h urinary epinephrine levels ($P < 0.05$), which returned to baseline by R+15.

Regarding circulating leukocytes and subsets, a large increase ($P = 0.07$) in WBCs and neutrophils were found 4 h after simulated launch (**Fig. 4**). Leukocytes then returned to baseline levels throughout the remainder of the bed rest. At 4 h after simulated landing, a significant increase ($P < 0.05$) in WBCs and neutrophils was again observed. **Fig. 5** shows the changes in monocytes and eosinophils. Monocytes were marginally increased at simulated landing ($P = 0.07$). Eosinophils displayed the opposite trend and were significantly decreased 4 h after simulated landing ($P < 0.05$).

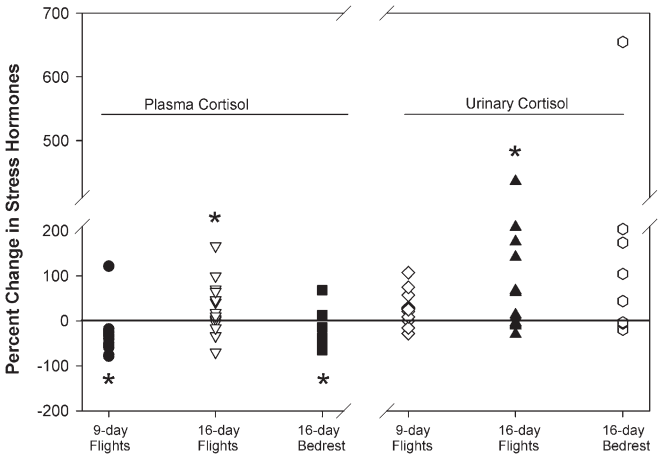

Fig. 2. Changes in plasma and urinary cortisol after a 9-d space mission ($n = 16$), a 16-d space mission ($n = 12$), and a 16-d bed rest ($n = 10$). Percent change in cortisol at landing (R+0) is expressed as the difference compared with individual preflight (L-10) values. *$P < 0.05$.

DISCUSSION

Few bed rest studies have investigated changes in the immune system. The longest bed rest to date has been 370 d involving nine subjects (13,23); immunological changes included decreases in NK cell function, decreased blast transformation, decreased antiviral immunity, and increased numbers of T- and B-lymphocytes in the peripheral circulation. Gmunder et al. (10) studied six male subjects and found that plasma cortisol was elevated before and during a 10-d head-down tilt bed rest; lymphocyte responsiveness was also severely reduced during this study. Other bed rest models have also shown increased IL-1 production (which may affect bone resorption) and decreased IL-2 production along with changes in leukocyte subset distribution and altered neutrophil and macrophage function (25). Although the changes in these studies are similar to those observed during spaceflight, none of them attempted to introduce gravitational forces associated with spaceflight. In order to test countermeasures across a broad number of physiological systems, it is paramount to have a model that encompasses as many of the characteristics of spaceflight as possible.

Notably, this model reproduced several important findings observed during spaceflight. Because the majority of current immunological data is pre/postflight, we first compared the simulated landing results to those found after actual spaceflights in order to validate this

TABLE I. COMPARISON OF LEUKOCYTE[a] AND LYMPHOCYTE[b] SUBSETS AFTER SPACEFLIGHT AND BED REST WITH REALISTIC G PROFILES.

	L-10			R+0		
	9 d Flt	16 d Flt	16 d BR	9 d Flt	16 d Flt	16 d BR
WBCs	5335 ± 347	5185 ± 284	5690 ± 495	8300 ± 491*	7242 ± 565*	9550 ± 1327*
Neutrophils	3145 ± 348	2858 ± 210	3328 ± 407	6186 ± 405*	4917 ± 523*	6806 ± 985*
Lymphocytes	1533 ± 101	1648 ± 141	1562 ± 188	1536 ± 159	2123 ± 343	2064 ± 137*
Monocytes	450 ± 42	429 ± 32	401 ± 56	498 ± 59	382 ± 64*	549 ± 61*
Eosinophils	189 ± 26	188 ± 31	167 ± 38	58 ± 22*	159 ± 47	95 ± 18*
$CD3^+CD4^+$	31 ± 6	46 ± 4	43 ± 2	42 ± 6*	49 ± 4	51 ± 3*

[a]White blood cell counts and differentials were performed on 10 bed rest subjects and 28 crewmembers ($n = 16$ for 9-d missions, $n = 12$ for 16-d missions). Values are mean ± SE (cells/mm^3). [b]Phenotypic analysis of lymphocyte subsets was performed on one 9-d flight ($n = 5$ crewmembers), one 16-d flight ($n = 6$ crewmembers), and 10 bed rest subjects. Values are percentage ± SE of total cells analyzed. *$P < 0.05$.

model. Similar to our 9-d flight data, urinary cortisol was elevated while plasma cortisol was decreased. These contradictory findings can be explained by the short half-life (< 90 min) of cortisol in blood (12). It is likely that increased G forces during landing or simulated landing provided a stimulus for cortisol release, but due to the brief nature of the stimulus, the "window" to detect increased blood cortisol levels was also fairly short. By measuring 24-h urine voids, which provides an integrated measure of cortisol over time, we were able to show that cortisol was increased.

Regarding leukocyte and lymphocyte subsets, the increase in WBCs were likely due to the increase in neutrophils. In addition, monocytes were increased while eosinophils were decreased. Consistent with our 9-d flights, increased catecholamine levels at simulated landing were associated with greater elevations in neutrophils (31). These hormonal responses and stress-induced shifts in circulating leukocytes are consistent with prior spaceflight studies (19,22,31). Past studies have demonstrated a causal relationship between stress hormones and changes in leukocyte and lymphocyte subpopulations (5,9), so it is likely that the changes in peripheral blood leukocytes are also due in part to elevated stress hormones. Moreover, the divergent patterns of neutrophils, monocytes, and eosinophils after centrifugation argue against simple hemoconcentration as a possible explanation for the redistribution of circulating leukocytes. Future studies that include pharmacological inhibitors of stress hormone release will be required to confirm the role of stress hormones as the primary mediator of leukocyte and lymphocyte changes.

Another important characteristic of spaceflight was also reproduced with this model. Specifically, an acute spike in cortisol was observed after simulated launch and cortisol continued to be elevated throughout the bed rest phase. These data are in agreement with prior Shuttle results (15,29). Interestingly, monocytes and lymphocytes were increased at simulated landing at which time cortisol was increased; this is somewhat of a paradox since administration of glucocorticoids typically produces a marked monocytopenia and lymphopenia (9). However, it is plausible that continuous exposure to elevated cortisol resulted in a state of "tolerance" that down-regulated adhesion molecules, resulting in a lack of migration through the vasculature; this would be consistent with our prior spaceflight results (29).

It is important to note that the increased levels of cortisol during flight have been linked to latent herpes virus reactivation in astronauts (21,29) and is consistent

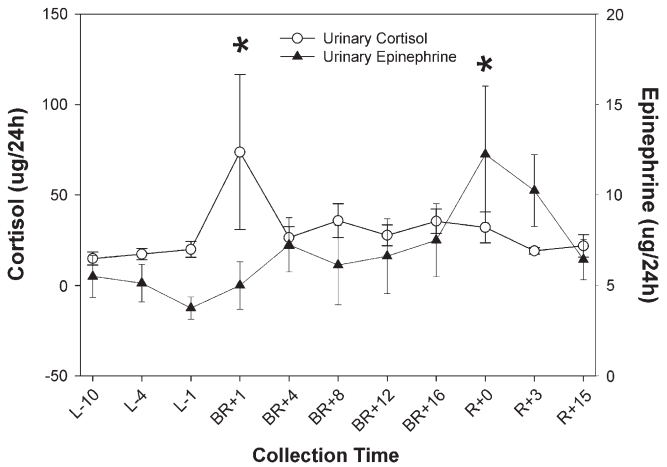

Fig. 3. Changes in 24-h urinary cortisol and epinephrine before, during, and after simulated spaceflight. *$P < 0.05$.

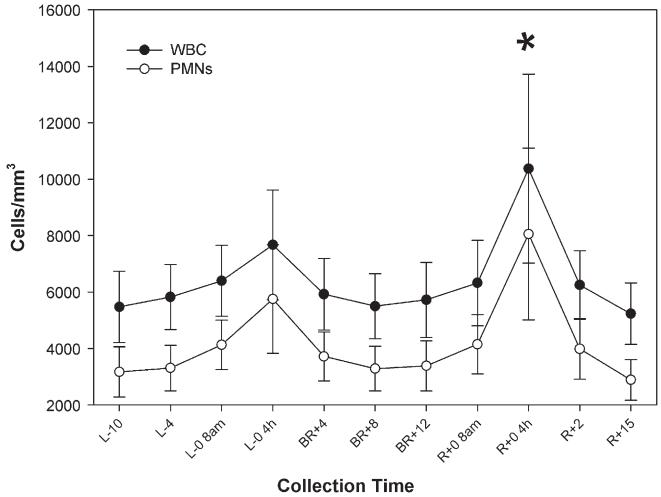

Fig. 4. Changes in white blood cell (WBC) counts and polymorphonuclear neutrophils (PMNs) before, during, and after simulated spaceflight. Both WBCs and PMNs were significantly elevated 4 h post "landing" (*$P < 0.05$).

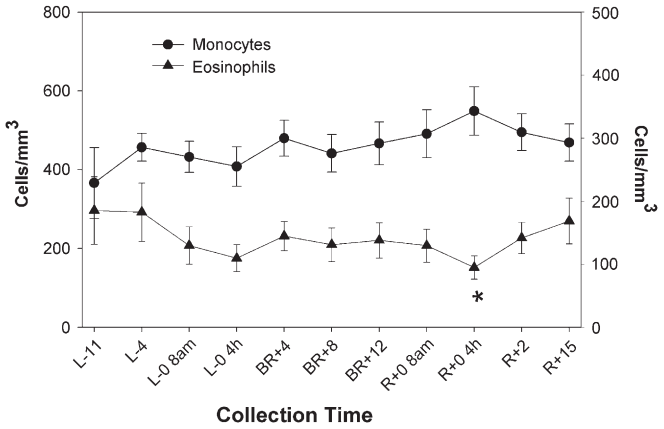

Fig. 5. Changes in monocytes and eosinophils during simulated spaceflight. A significant decrease in eosinophils and a nonsignificant increase in monocytes ($P = 0.07$) was found 4 h post "landing."

with glucocorticoid-mediated reactivation of herpes viruses in vitro (14,26). Notably, glucocorticoids are primarily anti-inflammatory in that they inhibit IL-12 production and increase IL-10 production by monocytes (4,7,8). This drives the immune response toward a Th2 cytokine profile (characterized by production of IL-4, IL-5, and IL-10, which elicits humoral immunity) and away from a Th1 profile (production of IL-2, IL-12, and IFN-γ, which elicits cellular immunity). This proposed shift is highly consistent with prior spaceflight findings of increased IL-10 during the first few days of flight (28) as well as increased synthesis of IgE (29,31). One mechanism by which glucocorticoids achieve this Th1-to-Th2 switch is by increasing the production of I-kB, which binds to the transcription factor NF-kB and inhibits translocation to the nucleus (1,24). NF-kB is a ubiquitous multiprotein complex involved in the transcriptional activation of several host defense genes including the cytokines IL-2, IL-6, IL-8, and IL-12 (3). Thus, dysregulation of the NF-kB pathway may be one mechanism behind the spaceflight-induced alterations in immune responses.

In summary, our results indicate that one major force behind immune changes associated with shorter duration Shuttle missions are the launch and landing stressors, in particular G forces. Unexpectedly, results from our bed rest studies more closely reflected data from 9-d Shuttle missions instead of 16-d Shuttle missions. We attribute this to the fact that physiological changes (e.g., muscle, neuroendocrine, etc.) during bed rest occur as a result of inactivity, whereas physiological changes in space result from true microgravity as well as other variables (e.g., isolation, sleep deprivation, noise and vibration, etc.). Since the underlying causes between the two are different, it can be expected that magnitude of bed rest associated changes will not completely match that of actual spaceflight within the same time period. However, the length of bed rest can be extended in future studies to model longer duration Shuttle missions or even stays aboard the International Space Station. Importantly, this model can be used to study multiple physiological systems (i.e., neuroendocrine, bone, muscle, immunity, etc.) under simulated spaceflight, and therefore the design and application of specific countermeasures can be evaluated on non-target systems.

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