Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight

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Medical Sciences Division, National Aeronautics and Space Administration Johnson Space Center, and KRUG Life Sciences, Houston, Texas 77058; and Centre for Advanced Technology Education, Ryerson Polytechnic University, Toronto, Ontario, Canada M5B 2K3

Fritsch-Yelle, Janice M., Peggy A. Whitson, Roberta L. Bondar, and Troy E. Brown. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. J. Appl. Physiol. 81(5): 2134–2141, 1996.—Postflight orthostatic intolerance is experienced by virtually all astronauts but differs greatly in degree of severity. We studied cardiovascular responses to upright posture in 40 astronauts before and after spaceflights lasting up to 16 days. We separated individuals according to their ability to remain standing without assistance for 10 min on landing day. Astronauts who could not remain standing on landing day had significantly smaller increases in plasma norepinephrine levels with standing than did those who could remain standing (105 ± 41 vs. 340 ± 62 pg/ml; P = 0.05). In addition, they had significantly lower standing peripheral vascular resistance (23 ± 3 vs. 34 ± 3 mmHg·l−1·min; P = 0.02) and greater decreases in systolic (−28 ± 4 vs. −11 ± 3 mmHg; P = 0.002) and diastolic (−14 ± 7 vs. 3 ± 2 mmHg; P = 0.0003) pressures. The presyncopal group also had significantly lower supine (16 ± 1 vs. 21 ± 2 mmHg·l−1·min; P = 0.04) and standing (23 ± 2 vs. 32 ± 2 mmHg·l−1·min; P = 0.038) vascular resistance, supine (66 ± 2 vs. 73 ± 2 mmHg; P = 0.008) and standing (69 ± 4 vs. 77 ± 2 mmHg; P = 0.007) diastolic pressure, and supine (109 ± 3 vs. 114 ± 2 mmHg; P = 0.05) and standing (99 ± 4 vs. 108 ± 3 mmHg; P = 0.006) systolic pressures before flight. This is the first study to clearly document these differences among presyncopal and nonpresyncopal astronauts before and after spaceflight and also offer the possibility of preflight prediction of postflight susceptibility. These results clearly point to hypadrenergic responsiveness, possibly centrally mediated, as a contributing factor in postflight orthostatic intolerance. They may provide insights into autonomic dysfunction in Earthbound patients.

METHODS

This protocol was approved by the Johnson Space Center Human Research Policy and Procedures Committee. Studies were conducted 30 and 10 days before launch, on landing day (1–2 h after landing), and 3 days after landing. On each test day, subjects had abstained from caffeine, alcohol, and any medications for the preceding 12 h; were at least 2 h postprandial; and had not exercised heavily in 24 h. Subjects were instrumented for electrocardiogram, manual blood pressure (sphygmomanometer), beat-to-beat blood pressure (Finapres, Ohmeda, Inglewood, CA), and transcranial Doppler (Medasonic, Fremont, CA). An intravenous catheter was inserted into an antecubital vein. After a 20-min supine rest period, plasma volume was determined by using carbon monoxide rebreathing (6, 25, 28). A blood sample was drawn for norepinephrine, epinephrine, and plasma renin activity. Then two-dimensional and M-mode echocardiography were used to determine aortic cross-sectional diameter, and aortic flow was measured with continuous-wave Doppler ultrasound. Middle cerebral artery flow velocity was measured through the right or left temporal window with 2-MHz pulsed transcranial Doppler ultrasound (1). Measurements continued while the subjects remained supine for 5 additional min. Subjects were then assisted to a standing position by three investigators. Subjects were lifted by being grasped behind both shoulders while their feet were swept off the bed to minimize artifactual blood pressure changes with the effort of standing. The finger with the continuous arterial pressure

Virtually every astronaut returning from space suffers some degree of orthostatic intolerance. Returning astronauts exhibit signs and symptoms when subjected to upright posture that are similar to those in patients with orthostatic intolerance due to autonomic dysfunction. These include nausea, vomiting, lightheadedness (presyncope), and fainting (syncpope) (4). However, orthostatic hypotension in returning astronauts is spontaneously reversible, resolving without treatment in several days (10, 12, 30). The etiology of orthostatic intolerance after spaceflight is not yet understood. The known losses of plasma volume after spaceflight (19) have been thought to contribute to the problem. However, in head-down bed rest studies (commonly employed on Earth to mimic the fluid changes associated with spaceflight (20)), restoration of plasma volume does not restore orthostatic tolerance (3). We have previously shown that a reduction in arterial baroreflex function after spaceflight is related to orthostatic intolerance (10, 12).

There is a wide range of individual susceptibility to orthostatic intolerance after spaceflight. Some individuals have severe symptoms, whereas others are less affected. These differences have not been explored. No preflight predictor of postflight orthostatic intolerance has been previously identified, nor have physiological differences between individuals who do and who do not experience severe symptoms (presyncope or syncpoe) on landing day been previously reported. The purpose of this study was to characterize differences in physiological responses of astronauts who are and who are not susceptible to orthostatic hypotension after spaceflight. We studied hemodynamic and neuroendocrine responses to orthostatic stress in 40 astronauts (8 women and 32 men), whose mean age was 40 ± 1 yr, before and after shuttle missions lasting 8–16 days. Analyses and discussion in this study focus not on preflight to postflight changes, which have been reported previously (4, 10, 12, 30), but rather on differences between those astronauts who did and those who did not become presyncopal on landing day.
device was held at heart level by a system of Velcro straps. Subjects remained standing without support for 10 min. A final blood sample was drawn at the end of the standing period. Subjects who became presyncopal were returned to a supine position, and blood samples were drawn immediately. All data were recorded on digital tape for later analyses. All analog signals were also recorded on paper.

On landing day, all subjects consumed the equivalent of at least 8 g of NaCl and 1 liter of water 1–2 h before landing (the standard fluid-loading procedure). Between landing and the time of the data collection, they drank an average of 556 ± 121 ml water (ranging from 0 to 1,895 ml).

Analyses. Comparisons of trends over the time of standing were not possible because the time of standing ranged from 1 to 10 min, depending on whether and when presyncopal symptoms intervened. The following variables were compared during the last minute supine and the last minute of standing: plasma norepinephrine, epinephrine, and renin activity (collected immediately on resumption of supine posture in presyncopal subjects on landing day); heart rate (electrocardiogram); arterial pressure (sphygmomanometer); stroke volume (Doppler ultrasound); cardiac output (stroke volume x heart rate); total peripheral resistance (mean arterial pressure/cardiac output); mean flow velocity in the middle cerebral artery (transcranial Doppler); and cerebral vascular resistance (mean arterial pressure at the level of the Circle of Willis/mean flow velocity).

Analyses of all signals were made off-line by using standard data-acquisition and -analyses packages. Plasma catecholamines were determined by using a radioenzymatic assay (5). Plasma renin activity was estimated from the production of angiotensin I (27). Angiotensin I was quantitated by radioenzymatic assay (Biotex Laboratories, Friendswood, TX).

Statistics. Of the 40 original astronaut subjects, 7 were excluded from analysis because they had taken promethazine or dextroamphetamine within 12 h or caffeine within 4 h preceding the test on landing day. Four were excluded from analyses because their blood samples were ruined in transport from the landing site. Of the remaining 29 astronauts, those who were presyncopal on landing day were grouped separately from those who were not, and intergroup differences were determined. All data were tested for normalcy (23). The effects of interest were group (presyncopal vs. nonpresyncopal) and day (preflight, landing day, 3 days after landing). A repeated-measures analysis of variance was used. Student's t-tests were performed to document differences in variables when there was a significant main effect.

RESULTS

Intergroup differences on landing day. On landing day, 8 of 29 subjects could not complete the test because presyncopal symptoms intervened. A landing day presyncopal incident is presented in Fig. 1. We have compared arterial pressure and heart rate responses during tilt in a patient with adrenergic failure (Fig. 1A) (24) with responses during stand tests before (Fig. 1B) and after (Fig. 1C) flight in an astronaut. Note the striking similarities between Fig. 1, A and C. Before flight, this astronaut subject had an increase in norepinephrine of 236 pg/ml on standing but on landing day had no measurable increase in norepinephrine on standing. All presyncopal incidents displayed this arterial pressure and heart rate pattern, with presyncopal symptoms intervening between 1 and 9 min after standing. There were no vasovagal incidents, and no subject lost consciousness.

Mean data for the last minute supine and last minute standing on landing day for all subjects are shown in Table 1. Also shown are the supine-to-standing differences for each variable. The most striking and fundamental intergroup difference was the significantly lower norepinephrine response in the presyncopal group, who had only one-third as great an increase with standing as did the nonpresyncopal group (P = 0.05). There was a significant group effect for peripheral vascular resistance (P = 0.005), and standing vascular resistance was one-third lower in the presyncopal group (P = 0.035). There was a significant group effect for diastolic pressure (P = 0.0001). In fact, diastolic pressure fell precipitously on standing in presyncopal subjects but
The nonpresyncopal group consisted of 2 women who were and those who were not destined to become high-performance aircraft before joining the astronaut corps (all of these were men). Groups did not differ in age, height, weight, or normal exercise routine. The subjects did not separate by in-flight symptoms. Some individuals from both groups experienced changes in taste and vision, constipation, urinary retention and/or incontinence, and foot oedema. Thirty-eight percent of the presyncopal group and 33% of the nonpresyncopal group reported no in-flight symptoms.

Intergroup differences before and 3 days after flight. Table 2 shows differences before launch between those who were and those who were not destined to become

<table>
<thead>
<tr>
<th>Variable</th>
<th>Presyncopal on Landing Day (n = 8)</th>
<th>Nonpresyncopal on Landing Day (n = 21)</th>
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<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Standing</td>
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<tr>
<td>Plasma norepinephrine, pg/ml</td>
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<tr>
<td>Peripheral vascular resistance, mmHg·l⁻¹·min</td>
<td>330 ± 67</td>
<td>420 ± 46*</td>
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<tr>
<td>Diastolic pressure, mmHg</td>
<td>16.0 ± 1.3</td>
<td>22.9 ± 2.5*</td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>74 ± 4</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>110 ± 4*</td>
<td>80 ± 3</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>72 ± 5*</td>
<td>114 ± 8</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>58 ± 3</td>
<td>5.3</td>
</tr>
<tr>
<td>Mean flow velocity (middle cerebral artery), cm/s</td>
<td>52.4 ± 4.7</td>
<td>40.0 ± 2.9</td>
</tr>
<tr>
<td>Cerebral vascular resistance, mmHg·cm⁻²·s⁻¹</td>
<td>1.7 ± 3.0</td>
<td>1.1 ± 0.1</td>
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<tr>
<td>Plasma epinephrine, pg/ml</td>
<td>4.7 ± 0.3</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Plasma renin activity, ng·ml⁻¹·h⁻¹</td>
<td>2.7 ± 1.2</td>
<td>3.4 ± 1.5</td>
</tr>
<tr>
<td>Plasma volume, liters</td>
<td>2.7 ± 0.2</td>
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Values are means ± SE; n, no. of subjects. Supine, standing, and standing-supine difference measurements for all variables (plasma volume was only measured supine) are separated into presyncopal and nonpresyncopal groups on landing day. *P < 0.05 between groups. †P < 0.01 between groups.

To reiterate, there were no vasovagal incidents. All presyncopal subjects showed an immediate collapse of arterial pressure on standing that did not recover before presyncope intervened. Figure 2 depicts peripheral vascular resistance with standing before flight in all subjects (Fig. 2A) and after flight in all presyncopal and four representative presyncopal subjects (Fig. 2B), showing the consistency of vascular resistance throughout the stand. There were no differences in peripheral vascular resistance from the first to the last minute of standing in either group, either preflight [30.5 ± 2.2 vs. 33.0 ± 2.4 mmHg·l⁻¹·min (P = 0.82) for the nonpresyncopal group and 21.2 ± 1.4 vs. 23.3 ± 1.7 mmHg·l⁻¹·min (P = 0.59) for the presyncopal group] or postflight [30.5 ± 2.1 vs. 33.8 ± 2.7 mmHg·l⁻¹·min (P = 0.79) for the nonpresyncopal group and 23.1 ± 3.8 vs. 21.5 ± 3.5 mmHg·l⁻¹·min (P = 0.18) for the entire presyncopal group].

Plasma volumes for both groups are shown in Tables 1, 2, and 3. No significant intergroup differences were found either before or after flight.

The presyncopal group consisted of 5 women and 3 men. The nonpresyncopal group consisted of 2 women and 19 men. One of the presyncopal group and 16 of the nonpresyncopal group had previously been pilots of high-performance aircraft before joining the astronaut corps (all of these were men). Groups did not differ in age, height, weight, or normal exercise routine. The subjects did not separate by in-flight symptoms. Some individuals from both groups experienced changes in taste and vision, constipation, urinary retention and/or incontinence, and foot oedema. Thirty-eight percent of the presyncopal group and 33% of the nonpresyncopal group reported no in-flight symptoms.

Intergroup differences before and 3 days after flight. Table 2 shows differences before launch between those who were and those who were not destined to become
presyncopal on landing day. Plasma norepinephrine levels were not different in subjects either supine or standing. Even so, supine and standing peripheral vascular resistances of the predetermined presyncopal group were significantly less than in the other group. Similarly, their supine and standing systolic and diastolic pressures and standing cerebral vascular resistance were all significantly lower, and supine and standing heart rates were higher, than those of the nonpresyncopal group. Their standing mean flow velocities in the middle cerebral artery also were higher. Thus the group destined to become presyncopal on landing day had functionally significant differences in cardiovascular responses before their entrance into the microgravity environment.

Mean responses of all subjects 3 days after landing are shown in Table 3. Results were similar to preflight. Subjects who had been presyncopal on landing day had significantly higher standing plasma norepinephrine, lower standing peripheral vascular resistance, lower supine and standing systolic and diastolic pressures, higher supine heart rate, and lower standing plasma epinephrine.

### Table 3. Measurements 3 days after landing

<table>
<thead>
<tr>
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<th>Presyncopal on Landing Day (n = 8)</th>
<th>Nonpresyncopal on Landing Day (n = 21)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Standing</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/ml</td>
<td>234 ± 36</td>
<td>552 ± 86*</td>
</tr>
<tr>
<td>Peripheral vascular resistance, mmHg·l⁻¹·min</td>
<td>16.3 ± 0.9</td>
<td>23.9 ± 0.9†</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>68 ± 2†</td>
<td>71 ± 4†</td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>110 ± 7*</td>
<td>96 ± 5†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 2*</td>
<td>83 ± 6</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>87 ± 8</td>
<td>54 ± 9</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.1 ± 0.3</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>Mean flow velocity (middle cerebral artery), cm/s</td>
<td>63.3 ± 7.2</td>
<td>57.0 ± 6.8</td>
</tr>
<tr>
<td>Cerebral vascular resistance, mmHg·cm⁻¹·s</td>
<td>1.4 ± 0.2</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Plasma epinephrine, pg/ml</td>
<td>18 ± 4</td>
<td>25 ± 4*</td>
</tr>
<tr>
<td>Plasma renin activity, ng·ml⁻¹·h⁻¹</td>
<td>1.9 ± 0.7</td>
<td>1.7 ± 0.8</td>
</tr>
<tr>
<td>Plasma volume, liters</td>
<td>3.5 ± 0.2</td>
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Values are means ± SE; n, no. of subjects. Supine, standing, and standing-supine difference measurements for all variables (plasma volume was only measured supine) separated into presyncopal and nonpresyncopal groups, three days after landing. *P < 0.05 between groups; †P < 0.01 between groups.
between preflight and 3 days after landing are presented in Fig. 4. Similar to what is presented in Table 3, the intergroup differences seen several days after landing have mostly returned to preflight status. There were no intergroup differences between responses preflight and 3 days after landing.

DISCUSSION

This study provides three insights into orthostatic hypotension after spaceflight. First, individuals have measurable differences in susceptibility to postspaceflight orthostatic hypotension. Second, presyncope on landing day is at least partially attributable to hypoadrenergic responses during upright posture. Third, there may be a preflight predisposition in the susceptible individuals. These findings not only suggest mechanisms of orthostatic tolerance following spaceflight but may also have clinical relevance. We describe reversible autonomic dysfunction that resolves without treatment within a few days. These results may have relevance to irreversible autonomic function in Earth-bound patients.

Hypoadrenergic responses on landing day. Subnormal increases in norepinephrine with upright posture

![Fig. 3. Landing day minus preflight changes in response to standing from a supine position compared between presyncopal and nonpresyncopal groups. Presyncopal group lost a large portion of their norepinephrine response to landing after spaceflight, whereas nonpresyncopal group had larger norepinephrine response to standing (A). Presyncopal group lost differentially more diastolic (C) and systolic pressures (D) when they stood after flight and had significantly greater increases in heart rate (E). n, No. of subjects. *P ≤ 0.05 between groups. †P ≤ 0.01 between groups.]

![Fig. 4. Three days postflight minus preflight changes in response to standing from a supine position compared between presyncopal and nonpresyncopal groups. There were no significant intergroup differences in the changes in responses to standing. n, No. of subjects.]

Presyncopal, (n = 8)
Nonpresyncopal, (n = 21)
indicate a functional change in the neurogenic feedback loop, which includes arterial baroreceptors, brainstem, spinal tracts, and sympathetic nerves. Normal supine, but subnormal standing, plasma norepinephrine levels are seen in patients with impaired central modulation of baroreceptor input, such as diabetes (33), cervical spinal cord transection (33), and the Shy-Drager syndrome (26, 33). On the other hand, patients with peripheral neuropathy usually have subnormal supine and subnormal standing norepinephrine levels (33). These data therefore suggest that human cardiovascular adaptations to microgravity include changes in central modulation of baroreceptor inputs that cause a hypoadrenergic response to orthostasis that results in presyncope in 25% of returning astronauts.

There are anecdotal data that have been reported before (12) that may indirectly support the idea of changes in central modulation of autonomic function. These are the various in-flight symptoms reported by astronauts during interviews. They include urinary retention and/or incontinence, diarrhea, constipation, changes in vision, taste, smell, thirst, and appetite, and hypesthesias and paraesthesias in the feet. These symptoms have not been investigated, but they may be relevant to an understanding of in-flight autonomic changes.

Differences between presynopal and nonpresynopal groups. These data not only suggest a mechanism for postflight orthostatic intolerance but also show clear differences between susceptible and nonsusceptible individuals and, for the first time, raise the possibility of predicting susceptible individuals before launch. The intergroup differences before flight suggest that there is a subset of the normal population who has orthostatic responses within normal ranges before flight but who is predisposed to postflight orthostatic intolerance. This group had norepinephrine responses to standing that were normal both before and 3 days after flight, but during every test session these subjects had lower vascular resistance and arterial pressures and higher heart rates than did those in the other group. This suggests possible prefight intergroup differences in venous compliance and/or vascular responsiveness. Spaceflight affects this group differentially. Whereas the nonsusceptible group had increased adrenergic responses to upright posture after flight, this group had a subnormal adrenergic response, which results in presyncope.

Influence of gender on orthostatic tolerance. This laboratory has performed stand tests on 91 astronauts who flew on the shuttle but were not in this study (17 women and 74 men). Of those, six women (35%) and five men (7%) became presynopal on landing day (J. M. Fritsch-Yelle, unpublished observations). The majority of the susceptible astronauts in the present study were career pilots of high-performance aircraft before they became astronauts. All the pilots were men. These people would not have been successful in that career if they did not have a high tolerance to G forces (either learned or inherent).

Cerebral autoregulation. The reductions in cerebral vascular resistance with standing we documented are consistent with the accepted concept of cerebral autoregulation (21). On landing day, the presynopal group showed a greater compensatory decrease in cerebralvascular resistance (vasodilation) in response to the greater fall in mean arterial pressure. However, this was not adequate to maintain mean flow velocity in the face of the collapse of systemic arterial pressure. Because both groups did not experience this calamitous fall in arterial pressure, no conclusions can be drawn about intergroup differences in cerebral autoregulation.

Other cardiovascular changes associated with spaceflight. This is not the first report of in-flight changes in autonomic regulation of cardiovascular function that affect postflight function. We previously reported attenuation of the vagally mediated carotid baroreceptor cardiac reflex response that begins as early as the 2nd day in flight and persists for ~1 wk postflight (10–12). On landing day, reductions in this reflex correlate directly with lower standing systolic pressures. We have also reported in-flight decreases in heart rate and arterial pressure that are reversed on landing day and in-flight decreases in frequency of cardiac dysrhythmias (13). Immediately after shuttle landing, we have reported standing heart rates as high as 160 beats/min, as the cardiovascular system struggles to support...
arterial pressure, yet systolic pressure can fall as much as 25 mmHg.

Unfortunately, no previous study has separated presyncopal and nonpresyncopal data for analyses. For example, although there are reports that in-flight catecholamines are low (C. L. Hunton, personal communication) and in-flight arterial pressures and heart rates are low (13), it has never been determined whether in-flight measurements are different in those who become presyncopal on landing day. Presumably they are. If in-flight sympathetic activity/catecholamines in presyncopal astronauts is differentially low, for example, an upregulation of adrenergic receptors might be expected. If postsynaptic $\alpha_2$-adrenergic receptors were upregulated, an increased resistance response would be expected. If, however, presynaptic $\alpha_2$-receptors are upregulated in this group, or central modulation is dysfunctional, norepinephrine release and peripheral resistance would be inhibited as in the present study. A previous study addressed this issue indirectly. Whitson et al. (30) showed that, in subjects on standing, the ratio of increase in total peripheral resistance, indicating that the increase in norepinephrine was reduced on landing day, indicating that $\alpha_1$-receptors probably were not upregulated. However, presyncopal and nonpresyncopal subjects were not separated in that study. These issues have not been resolved.

Role of differences in plasma volume. These results do not support the notion that loss of plasma volume is a primary cause of postflight orthostatic hypotension. These data support previous findings from bed rest studies that show that restoration of plasma volumes did not restore post-bed rest orthostatic tolerance (3).

Limitations. When subjects in this study became presyncopal before the end of 10 min of standing, they were returned to the supine position for the final blood draw. We were concerned that plasma norepinephrine levels in this group may have been low partially as a result of their decreased time in the upright posture. To address this concern, we repeated the stand test protocol in the laboratory by using 11 normal volunteers (3 women, 8 men) who had not flown in space. We drew blood samples for norepinephrine analysis after 2, 4, 6, 8, and 10 min of standing, rather than only at the end. All subjects had passed the same Air Force class III physical that the astronauts must pass. The volunteers’ mean age was 31 ± 2 yr. These subjects experienced both sys- tolic and diastolic pressure decreases of only 1 ± 1 mmHg during standing. The changes in norepinephrine levels at 2, 4, 6, 8, and 10 min of standing for these laboratory subjects were 48 ± 7, 60 ± 8, 178 ± 7, 205 ± 5, and 190 ± 6 pg/ml. When these data were compared with landing day norepinephrine levels in presyncopal astronauts, six of the eight presyncopal astronauts had norepinephrine responses at the time of their presyncope that were below those in the normal group after the same duration of standing. Thus, even though they experienced tremendous arterial pressure falls (Table 1), they still did not have norepinephrine responses as great as those in normal subjects who had not been in space and were not experiencing arterial pressure declines.

In summary, we studied the integrated responses to standing in astronauts before and after spaceflight. We found that there are some who are more susceptible to orthostatic intolerance immediately after spaceflight (characterized by hypoadrenergic responses to upright posture), who recover spontaneously within a few days, and who show a preflight predisposition to this susceptibility. These findings may have significance for Earthbound patients with orthostatic hypotension as well as for space travelers.

We are indebted to the astronauts who participated in this study. We also thank the personnel in the Cardiovascular and Biochemistry Laboratories at Johnson Space Center and the Laboratory at the Centre for Advanced Technology Education at Ryerson Polytechnic University in Toronto for their tireless efforts in accomplishing this project. We also thank Michael G. Ziegler for his contribution of the enzymes for the catecholamine analyses and critical review of the manuscript and Urs A. Leuenberger for assistance in echocardiography on landing days.

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